Moyamoya disease case series

2024

The clinical and radiologic data of moyamoya disease cases were accessed from medical and radiological records between January 2010 and July 2017. Two neuroradiologists independently analyzed the data and imaging details. Out of 103 patients with MMD, eight patients (7.77%) had associated intracranial aneurysms with eleven aneurysms. Out of the 11 aneurysms, five were the tip of the basilar artery aneurysms and were the most common location for aneurysm (45.5%), followed by lenticulostriate artery, PCA perforator, and distal ACA (DACA) in the P1 PCA, P2 PCA, and P3 PCA artery aneurysms. Out of eight patients, five (62.5%) had a hemorrhage on a non-contrast computed tomography (NCCT) scan of the brain, whereas three (37.5%) had an ischemic presentation. Out of 11 aneurysms, seven aneurysms, including three basilar tip aneurysms (unruptured) and one PCA perforator (ruptured), and three saccular PCA (P1, P2, and P3) (ruptured) were treated by endovascular coiling. Follow-up angiography showed stable aneurysmal occlusion except in one basilar tip, where recurrence was observed. MMD-intracranial aneurysm is commonly observed in patients with intracranial hemorrhage and carries a higher risk of rupture. Therefore, identification of the aneurysm is essential for management. Endovascular treatment, either with coil or glue embolization, can be a safe and effective treatment method for such aneurysms with long-term good results [1)].

2023

A nationwide retrospective cohort study encompassed patients with MMD registered under the Rare Intractable Diseases program via the Relieved Co-Payment Policy between 2006 and 2019, using the Korean National Health Insurance Service database. Following a 4-year washout period, landmark analyses were employed to assess mortality and stroke occurrence between the bypass surgery group and the nonsurgical control group at specific time points post-index date (1 month and 3, 6, 12, and 36 months). The study included 18 480 patients with MMD (mean age, 40.7 years; male to female ratio, 1:1.86) with a median follow-up of 5.6 years (interquartile range, 2.5-9.3; mean, 6.1 years [SD, 4.0 years]). During 111 775 person-years of follow-up, 265 patients in the bypass surgery group and 1144 patients in the nonsurgical control group died (incidence mortality rate of 618.1 events versus 1660.3 events, respectively, per 105 person-years). The overall adjusted hazard ratio (HR) revealed significantly lower all-cause mortality in the bypass surgery group from the 36-month landmark time point, for any stroke mortality from 3- and 6-month landmark time points, and for hemorrhagic stroke mortality from the 6-month landmark time point. Furthermore, the overall adjusted HRs for hemorrhagic stroke occurrence were beneficially maintained from all 5 landmark time points in the bypass surgery group. Conclusions Bypass surgery in patients with MMD was associated with a lower risk of all-cause and hemorrhagic stroke mortality and hemorrhagic stroke occurrence compared with nonsurgical control [2)].

A multicentre, prospective study enrolled adult patients with MMV from Huashan Hospital, Fudan University and National Center for Neurological Disorders, China between March 2021 and February 2022. Multimodal neuroimages containing structural and functional information were used to evaluate

personalised disease severity and fused to localise the surgical field, avoid invalid regions and propose alternative recipient arteries. The recipient artery was further selected intraoperatively by assessing regional haemodynamic and electrophysiological information. The preanastomosis and postanastomosis data were compared with assist with the postoperative management. Patients who received such tailored revascularisations were included in the novel group and the others were included in the traditional group. The 30-day surgical outcomes and intermediate long-term follow-up were compared.

Results: Totally 375 patients (145 patients in the novel group and 230 patients in the traditional group) were included. The overall complication rate was significantly lower in the novel group ($p<0.001$). In detail, both the rates of postoperative infarction (p=0.009) and hyperperfusion syndrome (p=0.010) were significantly lower. The functional outcomes trended to be more favourable in the novel group, though not significantly (p=0.260). Notably, the proportion of good functional status was higher in the novel group (p=0.009). Interestingly, the preoperative statuses of perfusion and metabolism around the bypass area were significantly correlated with the occurrence of postoperative complications ($P<0.0001$).

Conclusions: This novel evaluating system helps to identify appropriate surgical field and recipient arteries during bypass surgery for MMV to achieve better haemodynamic remodelling and pathophysiological improvement, which results in more favourable clinical outcomes [3].

2022

Seventy Moyamoya disease patients (50 years old ± 9, 30 males).

Field strength/sequence: Time-resolved three-directional velocity encoded fast field echo sequence (4D flow) MRI, T1-weighted fast field echo sequence, T2 weighted turbo spin echo sequence, diffusion-weighted echo planar imaging; T2-weighted fluid-attenuated inversion recovery turbo spin echo sequence, susceptibility-weighted fast field echo sequence and time-of-flight MR angiography fast field echo sequence at 3.0T.

Assessment: ICA hemodynamics (maximum and average velocity [Vmax , Vavg], average blood flow [Flowavg], and wall shear stress) were analyzed based on 4D flow data. Cerebral infarction, defined as the occurrence of events, in 124 brain hemispheres was determined according to clinical symptoms and conventional brain MR imaging.

Statistical tests: The independent-sample T test was used to evaluate differences in ICA hemodynamics between infarcted and non-infarcted hemispheres. Binary logistic regression was performed to investigate the relationship between ICA hemodynamics and events. A P value < 0.05 was considered statistically significant.

Results: Sixty-one infarcted hemispheres (eight hemispheres with acute ischemic damage, 30 with chronic ischemic damage, and 23 with chronic hemorrhagic damage) had cerebrovascular events and 63 non-infarcted hemispheres did not. The hemodynamic parameters in the infarcted hemispheres (Vmax : P < 0.001; Vavg : P = 0.003; and Flowavg : P = 0.004) were significantly lower than those in the non-infarcted hemispheres. However, Vmax (P = 0.052), Vavg (P = 0.107), and Flowavg (P = 0.074) were not significantly different among hemispheres with acute ischemic lesions, chronic ischemic lesions and chronic hemorrhagic lesions. Vmax (odds ratio 3.033, 95% CI: 1.075-8.562) was independently associated with cerebrovascular events.

Data conclusion: Vmax may be a higher risk factor for cerebrovascular events in MMA patients.

Evidence level: 2 TECHNICAL EFFICACY STAGE: 3 [4)]

Thirty-one patients with moyamoya (26 females; age = 45 ± 13 years; 41 revascularized hemispheres).

Anatomical MRI, hypercapnic CVR MRI, and DSA were acquired pre-surgically in adult moyamoya participants scheduled for clinically indicated surgical revascularization. One-year post-surgery, DSA was repeated to evaluate collateralization.

Field strength: 3 T.Sequence: Hypercapnic T2 -weighted gradient-echo blood-oxygenation-level-dependent, T2 -weighted turbo-spin-echo fluid-attenuated-inversion-recovery, T1 -weighted magnetization-prepared-rapid-gradient-echo, and T2 -weighted diffusion-weighted-imaging.

Assessment: Presurgical maximum CVR and response times were evaluated in VBA flow territories. Revascularization success was determined using an ordinal scoring system of neoangiogenic collateralization from postsurgical DSA by two cerebrovascular neurosurgeons (R.V.C. with 8 years of experience; M.R.F. with 9 years of experience) and one neuroradiologist (L.T.D. with 8 years of experience). Stroke risk factors (age, sex, race, vasculopathy, and diabetes) were recorded.

Statistical tests: Fisher's exact and Wilcoxon rank-sum tests were applied to compare presurgical variables between cohorts with angiographically confirmed good (>1/3 middle cerebral artery [MCA] territory revascularized) vs. poor (<1/3 MCA territory revascularized) outcomes.

Significance: two-sided $P < 0.05$. Normalized odds ratios (ORs) were calculated.

Criteria for good collateralization were met in 25 of the 41 revascularized hemispheres. Presurgical normalized VBA flow-territory CVR was significantly higher in those with good (1.12 ± 0.13 unitless) vs. poor (1.04 ± 0.05 unitless) outcomes. Younger (OR = -0.60 ± 0.67) and White (OR = -1.81 ± 1.40) participants had highest revascularization success (good outcomes: age = 42 ± 14 years, race = 84% White; poor outcomes: age = 49 ± 11 years, race = 44% White).

Presurgical MRI measures of VBA flow-territory CVR are highest in moyamoya participants with better angiographic responses to surgical revascularization.

Level of evidence: 1 TECHNICAL EFFICACY STAGE: 4 [5)].

2021

The study of Yamamoto et al. included 92 hemispheres of 61 patients who underwent Superficial temporal artery to middle cerebral artery bypass for moyamoya disease combined with encephalo-myo-duro-arterio-pericranial synangiosis (EDMAPS) between 2013 and 2019. There were 17 children and 44 adults. They retrospectively analyzed the findings on cerebral angiography before and 3 to 6 months after surgery, including Suzuki staging, the development of surgical collaterals, and the extent of abnormal collateral channels such as lenticulostriate, thalamic, and choroidal channels.

Following surgery, no pediatric and adult patients experienced any stroke during follow-up periods (40.2±25.5 and 54.9±19.7 months, respectively). Suzuki's stage significantly advanced in both adult

and pediatric patients after surgery (P=0.042 and P<0.001). In adult patients, all of the lenticulostriate, thalamic, and choroidal channels significantly regressed after surgery (P<0.001, P=0.012, and P=0.004, respectively). In pediatric patients, however, lenticulostriate and choroidal channels significantly regressed (P=0.005 and P=0.034, respectively). Correlation analysis revealed that the development of surgical collaterals determined the postoperative regression of choroidal channels (P<0.001).

STA-MCA anastomosis and EDMAPS may be one of the most effective procedures to widely provide surgical collaterals to the operated hemispheres and prevent not only ischemic but also hemorrhagic stroke by regressing the hemorrhage-prone abnormal collateral channels in MMD [6].

2020

Li et al. retrospectively reviewed 144 adult patients with Moyamoya disease who underwent 186 procedures of combined revascularization from March 2013 to July 2019. Clinical features and outcomes were analyzed, in particular regarding cerebral infarction and hyperperfusion syndrome (HPS). All of the patients received individualized management perioperatively, especially about the blood pressure management according to the characteristics of moyamoya disease.

Postoperative cerebral infarction and HPS within 14 days after revascularization were recorded. Cerebral infarction occurred in four (2.1%) procedures among four patients. No patients suffered from a malignant cerebral infarction and only one patient had permanent neurological deficits. The incidence of HPS was 10.8% and no one presented with intracranial hemorrhage. All of the symptoms were reversible without any brain parenchymal injury.

The findings suggest that we can decrease the incidence and extent of cerebral infarction in adult MMD patients following combined revascularization by individualized perioperative BP management [7].

Cerebral hyperperfusion syndrome (CHS) is a common complication after direct bypass surgery in patients with Moyamoya disease (MMD). Since preventive measures may be inadequate, Yang et al. assessed whether the blood flow difference between the superficial temporal artery (STA) and recipient vessels (△BF) and the direct perfusion range (DPR) are related to CHS.

They measured blood flow in the STA and recipient blood vessels before bypass surgery by transit-time probe to calculate △BF. Perfusion changes around the anastomosis before and after bypass were analyzed with FLOW 800 to obtain DPR. Multiple factors, such as △BF, DPR, and postoperative CHS, were analyzed using binary logistic regression.

Results: Forty-one patients with MMD who underwent direct bypass surgery were included in the study. Postoperative CHS symptoms occurred in 13/41 patients. △BF and DPR significantly differed between the CHS and non-CHS groups. The optimal receiver operating characteristic (ROC) curve cut-off value was 31.4 ml/min for ΔBF, and the area under the ROC curve (AUC) was 0.695 (sensitivity 0.846, specificity 0.500). The optimal cut-off value was 3.5 cm for DPR, and the AUC was 0.702 (sensitivity 0.615, specificity 0.750).

Postoperative CHS is caused by multiple factors. △BF is a risk factor for CHS while DPR is a protective factor against CHS [8].

84 consecutive patients diagnosed with moyamoya disease at our hospital between April 2009 and July 2016. In each patient, two axial continuous slices of T2-weighed imaging at the level of the basal cistern, basal ganglia, and centrum semiovale were acquired. The image sets were processed by using code written in the programming language Python 3.7. Deep learning with fine tuning developed using VGG16 comprised several layers.

Results: The accuracies of distinguishing between patients with moyamoya disease and those with atherosclerotic disease or controls in the basal cistern, basal ganglia, and centrum semiovale levels were 92.8, 84.8, and 87.8%, respectively.

Akiyama et al. showed excellent results in terms of accuracy of differential diagnosis of moyamoya disease using AI with the conventional T2 weighted images. The authors suggest the possibility of diagnosing moyamoya disease using AI technique and demonstrate the area of interest on which AI focuses while processing magnetic resonance images [9].

The incidence of Moyamoya disease (MMD) in Europe is not well known. In those affected, the risk of brain hemorrhage is considered low. A study of Birkeland et al. aimed to investigate the incidence and clinical presentation of MMD in the Danish population.

Eligible patients were identified in the Danish National Patient Register from 1994 to 2017. They collected clinical and radiological data from individual patient records from neurological, neurosurgical, and pediatric units across Denmark. The diagnosis was validated according to established criteria. They also extracted basic demographic data on the cohort from the Danish Civil Registration System.

A total of 52 patients fulfilled the diagnostic criteria for MMD. Most cases were native Danes and only 15% of cases had an East Asian background. The ratio of female to male patients was 1.8, and the incidence had two peaks: one in childhood and another in young middle age. Until 2007, MMD was only diagnosed sporadically. From 2008 onwards, the incidence rate was 0.07 per 100 000 person-years (95% confidence interval 0.05-0.09 per 100 000 person-years). The most common mode of presentation was ischemic stroke (33%), followed by hemorrhage (23%), headache (17%), and transient ischemic attack ((14%).

MMD is rare in Denmark, but associated with a considerable risk of hemorrhage. Thus, MMD should be considered in the workup for ischemic as well as hemorrhagic stroke in children and middle-aged Caucasians [10].

Moyamoya disease in adults is a chronic, progressive disorder characterized by fine collateral vessel networks in the brain. The disorder can lead to negative mood and stress, which, left unresolved, may increase adverse health outcomes. yang et al. conducted a cross-sectional survey to examine the stress and mood of adults with moyamoya disease. Participants were recruited at a university hospital in Seoul, Korea. Data were collected through questionnaires and review of participants' electronic medical records. A total of 109 adult patients participated. Significant correlations were found between perceived stress, anxiety, and depression. Adults with moyamoya disease experience anxiety, depression, and stress-related to the risk of cerebral hemorrhage or ischemia, similar to patients with other cerebrovascular diseases. If uncontrolled, negative mood and stress can cause

adverse health outcomes. Health professionals caring for patients with moyamoya disease should carefully observe patients' stress and mood and develop interventions tailored to stages of the disease to help patients manage stress and mood. The study results provide baseline information for understanding the level of and the factors associated with stress and mood [11].

Liu et al. retrospectively analyzed 214 MMD patients from January 2014 to January 2016. Clinical characteristics and LMC status were compared between pediatric and adult patients. Leptomeningeal collateral (LMC) status was graded as good or poor depending on the retrograde flow from the posterior cerebral artery (PCA) on digital subtraction angiography (DSA).

A total of 83 pediatric and 131 adult (1:1.6) MMD patients were analyzed. Pediatric patients were more likely to experience a transient ischemic attack (81%), whereas adult patients were more likely to experience infarction (51%). Regarding the different MMD stages (the early, medium and advanced stages corresponded to Suzuki staging stages 1-2, 3-4, and 5-6, respectively), the prevalence of good LMC status was higher for pediatric patients than for adult patients in the early stage ($P = 0.047$) and the medium stage ($P = 0.001$), but there were no differences between these patient groups in the advanced stage ($P = 0.547$). Worse postoperative angiographic outcomes ($P = 0.017$) were found in adult patients than in pediatric patients in the medium stage. Poor LMC status had strong correlations with infarction ($P < 0.001$ and $P = 0.017$) and poor postoperative outcomes ($P = 0.003$ and $P = 0.043$) in both pediatric and adult patients.

Pediatric MMD patients have greater patency and a greater ability to establish good LMC status than adult patients, and poor LMC status has a strong correlation with severe clinical symptoms and poor postoperative outcomes. LMC status may be an important factor in the differences in clinical characteristics and prognosis between pediatric and adult MMD patients [12].

2019

Uchino et al. studied 71 hemispheres of 30 adults and 16 children with MMD who underwent combined direct and indirect revascularization. They quantitatively measured the calibers of the superficial temporal artery (STA), deep temporal artery (DTA), and middle meningeal artery (MMA) with MR angiography (MRA) source images and calculated the postoperative caliber change ratios (CCRs) to assess direct and indirect bypass development. These values were compared with the findings of digital subtraction angiography, in which revascularization areas were categorized into 3 groups (poor, good, and excellent).

In both adult and pediatric hemispheres, the median STA and DTA CCRs were higher in better-revascularization groups ($p < 0.05$), while MMA CCRs were not significantly different among the groups. Receiver operating characteristic analysis revealed that the cutoff STA CCRs of > 1.1 and > 1.3 were associated with good direct revascularization in adult and pediatric hemispheres, respectively. Cutoff DTA CCRs of > 1.6 and > 1.2 were associated with good indirect revascularization in adult and pediatric hemispheres, respectively. Considering these cutoff values, STA and DTA CCRs showed high median values, irrespective of age, severity of cerebrovascular reserve, disease stage, and disease-onset type.

Caliber changes in STAs and DTAs can be easily measured using MRA, and they could be indicators of direct and indirect bypass development. The dual development of a direct and indirect bypass was

most frequently observed in the context of a combined bypass procedure in both adults and children with MMD [13].

Lee et al. evaluated the blood pressure (BP) of pediatric MMD patients at their postsurgical appointment following the American Academy of Pediatrics clinical practice guideline on high BP, in which hypertension was defined as BP measurements higher than the value of age-, sex-, and height-specific 95th percentile of the general population from at least 3 separate visits. Growth of patients was determined using 2017 Korean National Growth Charts for children and adolescents. The cutoff value of the 95th percentile of BP was determined by referring to normative BP tables of Korean children and adolescents. A logistic regression model was used to assess the associations between patients' clinical characteristics and prevalent hypertension.

In total, 131 surgically treated pediatric MMD patients were included, of whom 38.9% were male and the median age at diagnosis was 8.0 years (range 1.2-15.0 years). The definition of hypertension was met in 38 patients, with a prevalence of 29.0% (95% CI 21.2%-36.8%). A tendency was observed for a higher prevalence of hypertension in male patients (31.4%), in patients with posterior cerebral artery (PCA) involvement (47.8%), and in cases in which infarction was shown on initial MRI (37.3%). Age at diagnosis (adjusted OR [aOR] 0.82, 95% CI 0.70-0.97), PCA involvement (aOR 3.81, 95% CI 1.29-11.23), body mass index (aOR 1.30, 95% CI 1.13-1.51), and years of follow-up since surgery (aOR 0.80, 95% CI 0.68-0.94) were related to systemic hypertension.

A high prevalence of hypertension was demonstrated in pediatric MMD patients. Therefore, adequate attention should be paid to reduce BP and prevent subsequent events [14].

Forty-three consecutive adult patients with bilateral Moyamoya disease (MMD) underwent unenhanced T1-weighted MRI, territorial arterial spin labeling (t-ASL), and unenhanced 3D Time-of-flight magnetic resonance angiography (3D-TOF-MRA). Clinical factors, including age, sex, hypertension, diabetes mellitus, hyperlipidemia, current smoking status, and history of taking aspirin, were gathered and stratified. Univariate logistic regression analyses were used to examine the relationship between various risk factors and the occurrence of preoperative hemorrhage. Stepwise multivariate logistic regression analyses were used to determine independent risk factors of preoperative hemorrhage in MMD.

Among the 86 MMD hemispheres, t-ASL revealed 137 perfusion territory shifts in 79 hemispheres. Five distinct categories of perfusion territory shifts were observed on t-ASL maps. The subtypes of perfusion territory shift on t-ASL maps were further subdivided into 2 different categories, group A and group B, in combination with findings on 3D-TOF-MRA. A perfusion territory shift attributable solely to the secondary collaterals was a potential independent risk factor for preoperative hemorrhage ($p = 0.026$; 95% CI 1.201-18.615; OR 4.729). After eliminating the influence of the secondary collaterals, the primary collaterals had no significant effect on the risk of preoperative hemorrhage ($p = 0.182$).

Territorial arterial spin labeling (t-ASL) could reveal comprehensive Moyamoya disease (MMD) cerebral blood perfusion and the vivid perfusion territory shifts fed by the unilateral ICA and ECA and bilateral vertebral arterys (VAs) in a noninvasive, straightforward, nonradioactive, and nonenhanced manner. 3D Time-of-flight magnetic resonance angiography (3D-TOF-MRA) could subdivide t-ASL perfusion territory shifts according to their shunt arteries. A perfusion territory shift attributable to the secondary collaterals is a potential independent risk factor for preoperative hemorrhage in MMD

patients. A perfusion territory shift fed by the primary collaterals may not have a strong effect on preoperative hemorrhage in MMD patients. These findings make the combined modalities of t-ASL and 3D-TOF-MRA a feasible tool for MMD disease assessment, management, and surgical strategy planning [15].

Among 74 patients with MMD undergoing STA-MCA anastomosis for 78 affected hemispheres, 60 adult patients comprising 64 hemispheres underwent serial quantitative CBF analysis by N-isopropyl-p-[123I] iodoamphetamine single-photon emission computed tomography after revascularization surgery. The local CBF was quantitatively measured at the site of anastomosis and the adjacent cortex before surgery, as well as on 1 and 7 days after surgery. Then, we investigated the incidence, clinical presentation, and risk factors of the WS phenomenon.

The WS phenomenon was evident in 7 patients (7/64 hemispheres; 10.9%) after STA-MCA anastomosis for adult MMD. None of the patients developed neurological deterioration due to the WS phenomenon, but 1 patient developed reversible ischemic change on diffusion-weighted imaging at the site of the WS phenomenon. Multivariate analysis revealed that a lower preoperative CBF value was significantly associated with the occurrence of the WS phenomenon (20.3 ± 7.70 mL/100 g/min in WS-positive group vs. 31.7 ± 8.81 mL/100 g/min in WS-negative group, p= 1.1 × 10-2).

The incidence of the WS phenomenon was as high as 10.9% after STA-MCA anastomosis for adult MMD. The clinical outcome of the WS phenomenon is generally favorable, but there is a potential risk for perioperative cerebral infarction. Thus, we recommend routine CBF measurement in the acute stage after revascularization surgery for adult MMD to avoid surgical complications, such as local cerebral hyperperfusion (CHP) and cerebral ischemia, caused by the WS phenomenon. Concomitant detection of the WS phenomenon with local CHP is clinically important because blood pressure reduction to counteract local CHP may have to be avoided in the presence of the WS phenomenon [16].

A total of 346 patients underwent 437 revascularization procedures and the mean follow-up period was 4.0 years. The incidence of perioperative stroke was 6.9%. Adult at onset (OR, 5.033; 95% CI, 1.447-17.506; P=0.011) and posterior cerebral artery (PCA) stenosis (OR, 3.364; 95% CI, 1.588-7.265; P=0.002) before surgery were predictors of perioperative stroke. The annual subsequent stroke rate beyond 30 days after surgery was 1.2 %. Subsequent stroke events almost occurred throughout the first 5 years after surgery in adults, while in children mainly occurred within the first 2 years after surgery. Age at onset (OR, 1.025; 95% CI, 1.003-1.048; P=0.023), ischemic stroke or TIA at presentation (OR, 2.703; 95% CI, 1.062-6.875; P=0.037) and PCA involvement (OR, 2.664; 95% CI, 1.462-4.854; P=0.001) were associated with higher risk of overall postoperative stroke. PCA involvement (OR, 2.62; 95% CI, 1.33-5.15; P=0.005), ICA supraclinoid segment occlusion (OR, 2.76; 95% CI, 1.27 -6.03; P=0.011) and elder age at onset (OR, 1.03; 95% CI, 1.01 -1.05; P=0.033) were predictive of unfavorable outcome.

Patients with ischemic-type MMD at elder age and severer angiopathy might be at higher risk of recurrent stroke and unfavorable outcome after revascularization [17].

A retrospective cohort study included 94 Japanese patients with Moyamoya disease who underwent direct or combined bypass for revascularization with the p.R4810K genotype determined. The

following phenotypic parameters were analyzed at disease onset and over a long-term period: age and initial presentation at onset, recurrent stroke after initial revascularization, and final modified Rankin Scale.

The p.R4810K genotype was significantly associated with the phenotype at onset, especially in younger patients. Over a median follow-up period of 100 months, recurrent stroke occurred in 6 out of 94 patients: none out of 5 patients with the homozygous variant, 5 out of 64 with the heterozygous variant, and 1 out of 25 in the wild-type group. There were no significant differences among the genotypes. In particular, recurrent cerebral hemorrhage occurred in 5 patients, all possessing the heterozygous variant. The log-rank test showed no difference between the genotypes in the stroke-free survival rate. Furthermore, the p.R4810K genotype was not associated with a poor functional condition.

The p.R4810K founder variant of RNF213 affects the phenotype at disease onset. However, the optimal revascularization may be effective, regardless of the genotype, even for the homozygous variant, which has been thought to be the most pathogenic. This genotype may not strongly influence the long-term clinical manifestations or poor prognosis in MMD [18].

Primary intraventricular hemorrhage (PIVH) occurs frequently in adult hemorrhagic moyamoya disease (MMD).

A study aimed to compare the baseline characteristics and outcomes of acute MMD-related and idiopathic PIVH.

Adult patients with acute MMD-related or idiopathic PIVH were retrospectively included. Baseline characteristics and outcomes at discharge were obtained and compared. Chi-square test, t-test, or rank-sum test were used in statistical analyses.

This study finally included 32 patients with acute MMD-related PIVH and 112 with acute idiopathic PIVH. Patients with acute MMD-related PIVH were significantly younger (53.3 ± 15.8 vs. 42.8 ± 12.2 years, P<0.001). The admission systolic blood pressure in patients with acute idiopathic PIVH was significantly higher (161.7 ± 30.9 vs. 134.6 ± 24.6 mmHg, P<0.001). Patients with acute idiopathic PIVH had significantly higher admission serum urea (5.68 ± 2.66 vs. 4.34 ± 1.62 mmol/l, P=0.008), cystatin C (0.97 ± 0.72 vs. 0.68 ± 0.16 mg/l, P=0.023), and uric acid (309.01 ± 105.97 vs. 242.24 ± 77.65 µmol/l, P=0.001). In patients with acute MMD-related PIVH, only one (3.1%) patient was dead at discharge. In contrast, a total of 22 (19.6%) patients with acute idiopathic patients died at discharge (P=0.027).

Comparing to patients with acute idiopathic PIVH, patients with acute MMD-related PIVH have younger age, lower blood pressure, and better renal function. Moreover, patients with acute MMD-related PIVH have lower short-term mortality [19].

2018

Eighteen Moyamoya disease (MMD) patients and ten healthy controls were enrolled in a study from Zhongnan Hospital of Wuhan University, China. 2-dimensional Phase contrast magnetic resonance imaging (PC-MRI) scans were conducted to quantify the flow rate of main supplying arteries including internal carotid artery (ICAs) and vertebral artery (VAs). Mean flow rate in these vessels was adopted

as the patient-specific boundary condition for the computational fluid dynamics (CFD) simulation of the Circle of Willis (CoW) in MMDs and controls. Pressure drop in both ICAs and their difference, wall shear stress and secondary flow in the carotid siphon of ICAs, and flow rate and size of posterior communicating arteries (PComAs) were compared between MMDs and controls. Four MMD patients underwent follow-up scans for longitudinal comparison.

PC-MRI data revealed significantly different flow rate in ICAs and VAs between MMDs and controls. CFD simulation demonstrated similar wall shear stress and similar secondary flow of both ICAs, but significantly higher pressure drop in the LICA, higher pressure drop difference (PDD) between LICA and RICA and higher flow rate in PComAs in MMDs as compared with controls. Significantly increased size of the LPComA in MMDs was also found. Furthermore, follow-up results confirmed that the combination of PDD, flow rate and size of PComAs has the potential to assist long-term prognosis after surgery.

PDD, flow rate and size of PComAs can be used to evaluate impairments in cerebrovascular reserve and indicate long-term prognosis in MMD [20].

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105 adult patients with hemorrhagic MMD from January 2007 to May 2011 were prospectively enrolled in this study. All patients underwent combined revascularization surgery on unilateral hemorrhagic hemispheres and were observed for at least 5 years.

After a median follow-up time of 77 months, 12 patients were lost to follow-up. Twelve of the remaining 93patients developed rebleeding, and 6 patients died. According to rebleeding sites, ipsilateral and contralateral rebleeding occurred in 6 and 6 patients, respectively. There was no significant difference between the two groups ($p>0.05$). The annual risks of overall, ipsilateral, and contralateral rebleeding were 1.1%, 0.62%, and 0.51%, respectively. Significant correlation was observed between improvement of anterior choroidal artery (AChA)-posterior communicating artery (PCoA) dilation or extension in the operated hemispheres and low risk of ipsilateral rebleeding ($p<0.05$). Progression of Suzuki stage in the non-hemorrhagic hemispheres was significantly associated with contralateral rebleeding ($p<0.05$).

Combined revascularization surgery may help prevent ipsilateral rebleeding in adult patients with hemorrhagic MMD by improvement of AChA-PCoA dilation and extension in the operated hemisphere. Progression of Suzuki stage in the non-hemorrhagic hemispheres was a strong predictor of subsequent contralateral rebleeding [21].

2017

A total of 220 patients were considered, including 143 patients who underwent direct bypass (DB) and 77 patients who underwent IB. After propensity score matching, 70 pairs were obtained. The median follow-up period was 40.5 months (range 14-75 months) in the DB group and 31.5 months (range 14-71 months) in the IB group ($p = 0.004$). Kaplan-Meier analysis showed that patients who received DB had a longer stroke-free time (mean 72.1 months) compared with patients who received IB (mean 61.0 months) ($p = 0.045$). Good neurological status (mRS score ≤ 2) was achieved in 64 patients in the DB group (91.4%) and 66 patients in the IB group (94.3%), but there was no significant difference ($p = 0.512$).

Although neurological function outcome was not determined by the surgical modality, DB is more

effective in preventing recurrent ischemic strokes than IB for adult ischemic-type MMD [22].

Zhao et al. reviewed the records of 696 consecutive moyamoya vasculopathy patients from 2009 to 2015. The Suzuki and the Miyamoto stages were used to evaluate the steno-occlusive lesions of the anterior and posterior arteries. Clinical and radiographic features were compared between those with and without PCA involvement, also between pediatric and adult patients. A total of 574 angiograms (140 pediatrics and 434 adults) were reviewed. The prevalence of PCA steno-occlusion did not differ significantly between pediatric patients and adult patients (35.0% vs. 30.4%, P = 0.347). Pediatric patients had more advanced PCA stages compared to adult patients (P = 0.045). There was a significant correlation of the PCA angiographic stages with the ipsilateral internal carotid artery (ICA) stages, both in pediatrics and in adults (both P < 0.001). The frequency of ipsilateral cerebral infarction positively correlated with the advancement of PCA stages in adult patients (P < 0.001), but not significant in pediatric patients (P = 0.106). Pediatric patients tend to have more advanced PCA lesions than adult patients. The degree of PCA steno-occlusion positively correlates with the ipsilateral ICA stage, both in pediatrics and in adults [23].

Zhao et al. reviewed 696 consecutive patients with moyamoya vasculopathy (155 pediatric patients and 541 adults) admitted to our hospital from 2009 to 2015 to identify pediatric patients with moyamoya with an initial presentation of TIA. We defined recurrent TIAs that involve more types of symptoms or symptom extensions as symptom progression. The risk factors for subsequent stroke were analyzed using time-to-event analyses.

We identified 60 pediatric patients with moyamoya who had presented with TIA (initial presentation age, 10.0 ± 3.5 years). Motor weakness (n = 51 [85%]) was the most common initial presentation. During follow-up, 55 patients (91.7%) had recurrent TIAs and 14 (23.3%) had subsequent strokes. We identified female gender (hazard ratio, 5.08; 95% confidence interval, 1.40-18.47; P = 0.01), Suzuki grade greater than 3 (hazard ratio, 4.01; 95% confidence interval, 1.16-13.82; P = 0.03), and symptom progression (hazard ratio, 5.31; 95% confidence interval, 1.65-17.14; P = 0.01) as independent predictors of future stroke events.

Transient ischemic attacks have a relatively high recurrence rate in children with moyamoya and are associated with subsequent stroke. We identified the female sex, Suzuki grade greater than 3, and symptom progression as independent predictors of future strokes [24].

Zhao et al. reviewed consecutive adolescent patients with moyamoya disease. Clinical features, surgical treatment and long-term outcomes were analyzed. Follow-up was performed by face-to-face or structured telephone interviews. Outcome measures were future stroke events. We performed univariate and multivariate time-to-event analyses to identify risk factors associated with future stroke events.

A total of 95 adolescent patients with moyamoya disease (age at onset, 13.1 ± 2.3 years) were included in this study. During follow-up, 12 patients (12.6%) had stroke events. We found that the patients who underwent direct/combined bypass had a significantly lower risk of future strokes [hazard ratio (HR), 0.16; 95% confidence interval (CI), 0.03-0.74; P = 0.019] compared to patients who underwent indirect bypass.

The results demonstrate that direct/combined bypass can be more effective in preventing future strokes than indirect bypass in adolescent patients with moyamoya disease [25].

One hundred fifty-seven hemispheres in 122 adult patients with MMD were examined by DSC-MRI to measure the regional relative cerebral blood volume (CBV) and relative mean transit time (MTT). The patients were divided into 4 groups based on their clinical presentations: a nonsymptomatic (NS), hemorrhagic (H), infarction (I), and transient ischemic attack (T) group. The regional CBV and MTT values were compared among the 4 groups.

The relative value of CBV was significantly higher in groups T and I than in the NS group ($P < .01$). The CBV of group H was higher than that of the NS group only in the frontal lobe cortex. There were no significant statistical differences among the 3 symptomatic groups. Prolongation of the MTT in comparison with the cerebellum (MTT delay) was significantly higher in groups T and I than in the NS group in all regions of the cerebral cortex ($P < .05$). The MTT delay was significantly lower in group H than in group T in the frontal lobe and the Rolandic area ($P < .05$).

Hemodynamic factors measured by DSC-MRI reflected the variable clinical presentations of patients with MMD. DSC-MRI is a useful modality for evaluating the clinical conditions of individual adult patients with MMD [26].

2016

The purpose of a study was to reveal the radiological features of the "cortical hyperintensity belt sign" in postoperative FLAIR images and to verify its relationship to transient neurological events (TNEs) and regional cerebral blood flow (rCBF).

A total of 141 hemispheres in 107 consecutive patients with moyamoya disease who had undergone direct bypass surgery were analyzed. In all cases, FLAIR images were obtained during postoperative days (PODs) 1-3 and during the chronic period (3.2 ± 1.13 months after surgery). The CHB sign was defined as an intraparenchymal high-intensity signal within the cortex of the surgically treated hemisphere with no infarction or hemorrhage present. The territory of the middle cerebral artery was divided into anterior and posterior parts, with the extent of the CHB sign in each part scored as 0 for none; 1 for presence in less than half of the part; and 2 for presence in more than half of the part. The sum of these scores provided the CHB score (0-4). TNEs were defined as reversible neurological deficits detected both objectively and subjectively. The rCBF was measured with SPECT using N-isopropyl-p-[123I]iodoamphetamine before surgery and during PODs 1-3. The rCBF increase ratio was calculated by comparing the pre- and postoperative count activity.

Cortical hyperintensity belt signs were detected in 112 cases (79.4%) and all disappeared during the chronic period. Although all bypass grafts were anastomosed to the anterior part of the middle cerebral artery territory, CHB signs were much more pronounced in the posterior part ($p < 0.0001$). TNEs were observed in 86 cases (61.0%). Patients with TNEs showed significantly higher CHB scores than those without (2.31 ± 0.13 vs 1.24 ± 0.16, $p < 0.0001$). The CHB score, on the other hand, showed no relationship with the rCBF increase ratio ($p = 0.775$). In addition, the rCBF increase ratio did not differ between those patients with TNEs and those without (1.15 ± 0.033 vs 1.16 ± 0.037, $p = 0.978$).

The findings strongly suggest that the presence of the CHB sign during PODs 1-3 can be a predictor of

TNEs after bypass surgery for moyamoya disease. On the other hand, presence of this sign appears to have no direct relationship with the postoperative local hyperperfusion phenomenon. Vasogenic edema can be hypothesized as the pathophysiology of the CHB sign, because the sign was transient and never accompanied by infarction in the present series [27].

Kazumata et al., analyzed 20 consecutive surgeries performed in 17 adults. Diffusion imaging in parallel with serial measurements of regional cerebral blood flow (rCBF) using SPECT was performed. Both voxel-based and region-of-interest analyses were performed, comparing neuroimaging parameters of postoperative hemispheres with those of preoperative hemispheres at 4 different time points within 2 weeks after surgery.

Voxel-based analysis showed a distinct topographic pattern of cerebral perfusion, characterized by increased rCBF in the basal ganglia for the first several days and gradually increased rCBF in the lateral prefrontal cortex over 1 week ($p < 0.001$). Decreased rCBF was also observed in the lateral prefrontal cortex, occipital lobe, and cerebellum contralateral to the surgical hemisphere ($p < 0.001$). Reduced fractional anisotropy (FA) and axial diffusivity (AD), as well as increased radial diffusivity (RD), were demonstrated in both the anterior and posterior limbs of the internal capsule ($p < 0.001$). Diffusion parameters demonstrated the greatest changes in both FA and RD on Days 1-2 and in AD on Days 3-6; FA, RD, and AD recovered to preoperative levels on Day 14. Patients with transient neurological deteriorations (TNDs), as compared with those without, demonstrated greater increases in rCBF in both the lateral prefrontal cortex and striatum as well as smaller FAs in the posterior limb of the internal capsule ($p < 0.05$).

The excessively increased rCBF and the recovery process were heterogeneous across brain regions, demonstrating a distinct topographic pattern during the initial 2 weeks following revascularization surgery in MMD. Temporary impairments in the deep white matter tract and immediate postoperative ischemia were also identified. The study results characterized postoperative brain perfusion as well as the impact of revascularization surgery on the brain microstructure. Notably, rCBF and white matter changes correlated to TNDs, suggesting that these changes represent potential neuroimaging markers for tracking tissue structural changes associated with hyperperfusion during the acute postoperative period following revascularization surgery for MMD [28].

2015

Of the 142 consecutive surgeries for moyamoya disease from 2008, Sakata et al., herein presented 2 cases of adult-onset moyamoya disease that manifested local vasogenic edema at the site of anastomosis without cerebral hyperperfusion; 1 in a 31-year-old woman presented with transient ischemic attack and the other in a 22-year-old man manifested as minor completed stroke. Both patients underwent superficial temporal artery-middle cerebral artery anastomosis, resulting in the formation of a reversible high-signal-intensity lesion at the site of anastomosis on T2-weighted images along with an increase in apparent diffusion coefficient values, whereas diffusion-weighted images showed no changes. Neither hyperperfusion nor hypoperfusion, as assessed by single-photon emission computed tomography with N-isopropyl[123I]-p-iodoamphetamine, was observed postoperatively. In light of the increased risk of the further progression of vasogenic edema to intracerebral hemorrhage, these patients were treated with prophylactic blood pressure lowering and the intravenous infusion of a free radical scavenger. They did not have any further cerebrovascular events during the follow-up period. Regional vasogenic edema without cerebral hyperperfusion, possibly due to cerebral ischemia/reperfusion injury, may be another novel entity that needs to be

considered as a potential complication after extracranial-intracranial bypass for moyamoya disease. Strict postoperative management should be used to avoid hemorrhagic transformation [29].

Mukerji et al., examined postoperative cerebral perfusion in 31 patients with MMD who underwent a direct EC-IC STA-MCA bypass. A Hemedex Q500 flow probe was placed in the frontal lobe adjacent to the bypass and connected to a Bowman cerebral perfusion monitor, and CBF data were statistically analyzed using JMP 8.0.2 software. Seven patients experienced a TNE after surgery in the left hemisphere (that is, after left-sided surgery), manifesting as dysphasia approximately 24 hours postoperatively and which had improved by 48 hours. No TNEs were observed after right-sided surgeries. Operative and postoperative CBFs in the left side with the TNE were compared with those in the left side with no TNE and on the right side.

A detailed analysis of 64,980 minute-by-minute flow observations showed that the initial postbypass CBF was higher on the left side where the TNEs occurred. This CBF increase was followed by a widely fluctuating pattern and a statistically significant and sharp drop in perfusion ($p < 0.001$, mean difference of CBF between groups, paired t-test) associated with a TNE not observed in the other 2 groups.

On the basis of the authors' initial observations, an early-onset altered pattern of CBF was identified. These findings suggest local hypoperfusion as the cause of the TNEs. This hypoperfusion may originate from competing blood flows resulting from impaired cerebral autoregulation and a fluctuating flow in cerebral microcirculation [30].

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