Clinical Neurology and Neurosurgery 186 (2019) 105505

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Predictors and clinical features of transient neurological events after combined bypass revascularization for moyamoya disease

Junlin Lu[a], Yahui Zhao[a], Li Ma[a], Yu Chen[a], Mingtao Li[a], Xiaolin Chen[a], Xun Ye[a], Rong Wang[a,b,c,e], Yuanli Zhao[a,b,c,d,e,*]

[a] Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, PR China
[b] China National Clinical Research Center for Neurological Diseases, Beijing, PR China
[c] Center of Stroke, Beijing Institute for Brain Disorders, Beijing, PR China
[d] Beijing Key Laboratory of Translational Medicine for Cerebrovascular Disease, Beijing, PR China
[e] Department of Neurosurgery, Peking University International Hospital, Beijing, PR China

ARTICLE INFO

Keywords:
Moyamoya diease
Transient neurological events
Combined bypass
Vascular disorders

ABSTRACT

Objective: Transient neurological events (TNEs) are frequently observed after revascularization surgery for moyamoya disease (MMD). However, clinical features and pathophysiology of TNEs in MMD are still unclear. This study was aimed to clarify the incidence and time course of TNEs and to determine the independent predictors of TNEs in MMD.

Patients and methods: A total of 195 hemispheres in 171 consecutive patients with MMD who had undergone combined direct and indirect bypass surgery were analyzed. Preoperative clinical characteristics and radiographic features were recorded. The incidence and clinical feature of postoperative TNEs were evaluated. Multivariate logistic regression analyses were performed to identify the risk factors for postoperative TNEs. Outcomes were compared between patients who had TNEs with those without TNEs at the time of discharge.

Results: Postoperative TNEs were detected in 40 (20.5%) of 195 operated hemispheres, including 17 (42.5%) aphasia, 9 numbness of the extremities (22.5%), 6 seizures (15%), 5 motor weakness (12.5%), 4 dysarthria (10%) and 6 others (15%). The incidence of TNEs was significantly higher in adult patients than in pediatric ones. Multivariate analysis revealed that female, left-sided surgery and the presence of the edematous lesion was an independent predictor of TNEs after surgery in MMD (OR, 3.0; 95% CI, 1.1–8.2; P = 0.03, OR, 2.9; 95% CI, 1.2–7.0; P = 0.02 and OR, 17.4; 95% CI, 5.7–53.0; P < 0.01, respectively). DSA stage (OR 0.05, 95% CI 0.0–0.5, p = 0.005; OR 0.08, 95% CI 0.0–0.4, p = 0.008), PCA involvement (OR 2.75, 95% CI 1.0–7.4, p = 0.046), left-sided surgery (OR 2.73, 95% CI 1.2–6.5, p = 0.022) and edematous lesion (OR 21.2, 95% CI 7.6–59.7, < 0.001) were significantly associated with TNE severity. Compared with patients without postoperative TNEs, no significant differences in mRS score between the two groups were detected.

Conclusions: Female, left-sided surgery and edematous lesion were independent risk factors for postoperative TNEs; the left-sided surgery and edematous lesion were also independently associated with the severity of TNE. Although patients with postoperative TNEs had worse neurological status during the perioperative period, postoperative TNEs had no associations with worse mRS score at the time of discharge.

1. Introduction

Moyamoya disease (MMD) is an uncommon cerebrovascular disorder characterized by progressive occlusion of the internal carotid artery (ICA) terminus and its main branches, leading to compromised cerebral perfusion and recurrent ischemic strokes [21]. Surgical revascularization was currently the most effective management for MMD as it provides re-establishment of cerebral blood flow and improves cerebral ischemia [8,16,18,25]. Among a variety of revascularization techniques, direct and combined bypass are the most efficient because they provide immediately increase in blood flow by anastomosis of extracranial to intracranial arteries [8,16,18,22].

However, transient neurological events (TNEs) are commonly observed after direct or combined revascularization surgery for MMD

* Corresponding author at: Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, No. 119, South Fourth Ring West Road, Fengtai District, Beijing, 100070, PR China.
E-mail address: zhaoyuanli@126.com (Y. Zhao).

https://doi.org/10.1016/j.clineuro.2019.105505
Received 2 July 2019; Received in revised form 24 August 2019; Accepted 28 August 2019
Available online 29 August 2019
0303-8467/

[1,2,9,13,20,29,37]. As reported by previous studies, TNEs developed in 15%–67.1% of MMD patients who underwent direct or combined bypass surgery [1,4,11,31,38]. The symptoms usually resolve within 7 days, but in some cases, symptoms may persist for more than 10 days [5,30]. It had been suggested that TNEs might be caused by local cortical hyperperfusion, hypoperfusion and watershed shift after revascularization [2,12,29]; however, the incidence of TNEs varies significantly among different reports, and the risk factors also remain unknown. In this study, we aimed to clarify the incidence, features, as well as predictors of postoperative TNEs in MMD patients.

2. Material and methods

2.1. Patient

Patients with MMD had undergone combined direct and indirect bypass surgery at Peking University International Hospital between October 2015 and April 2018 were enrolled in this study. Cases with evidence of postoperative infarction shown on MRI were excluded because the abnormal hyperintensity signal on which this study focused could not be clearly distinguished due to the infarction [9]. The diagnosis was made according to the guidelines set by the Research Committee on Moyamoya Disease of the Ministry of Health, Labor, and Welfare of Japan.

This study was approved by an Ethics Committee at Peking University International Hospital. Written informed consent was obtained from all patients.

2.2. Surgical procedures

The principles of the surgical strategies were as follows. First, the indication for revascularization was based on the guidelines set by the Japanese Ministry of Health and Welfare [33]. Revascularization surgery of the symptomatic and hemodynamically affected hemisphere was the preferred. Second, if the patient's symptoms were significantly relieved after the first surgery and the patient did not have symptoms that could be ascribed to the contralateral hemisphere, surgical treatment of the contralateral hemisphere was not considered. Otherwise, surgery on the contralateral hemisphere was performed.

All patients included in this study underwent a combined bypass of superficial temporal artery to the middle cerebral artery (STA-MCA) anastomosis and encephalo-duro-arterio-synangiosis [15,17]. Briefly, the anterior branch of STA was anastomosed to cortical MCA (M4) in the frontal operculum with 10-0 nylon. In the meantime, indirect procedures were performed by attaching the posterior branch of STA and dural flaps on the brain surface. During surgery, indocyanine green (ICG) angiography was conducted to evaluate the patency of the bypass.

2.3. Radiological examinations

All patients underwent digital subtract angiography (DSA) before surgery to make the diagnosis and evaluate cerebrovascular conditions. Suzuki stage was recorded as previously described [36]. Moyamoya vessels (MMVs) generated from ICA was classified as absent, fair, or abundant (Fig. 1). Status of proximal MCA and proximal ACA was determined as normal, stenosed, or occluded. The terminal branches of ACA and MCA were determined as good or poor. PCA involvement was classified as yes or no. DSA was divided into 3 stages depending on the presence of stenotic or occlusive lesions, intracranial collateral pathways, and extra- intracranial collaterals [19].

Magnetic resonance imaging (MRI) scan and diffusion-weighted images (DWI) were conducted in all patients before surgery to detect pre-existing lesion (previous infarction or hemorrhage) and computed tomography perfusion (CTP) were also conducted to evaluate preoperative cerebral blood flow (CBF).

After surgery, all patients received an MRI and CTP within 5 days after surgery. And we defined the cortical hyperintensity along with subcortical low-intensity on postoperative fluid-attenuated inversion recovery (FLAIR) images as the edematous lesion.

2.4. Postoperative management

All patients were strictly managed to avoid hypovolemia and hypotension. Systolic blood pressure was maintained between 110 and 130 mmHg. Adult patients with ischemic-type MMD started taking Aspirin 1 day after surgery, whereas pediatric patients and hemorrhagic-type MMD patients did not take aspirin postoperatively.

2.5. Definition of TNEs

TNEs were identified according to previous literature [9] as follows: 1) any reversible neurological deficits observed objectively (e.g., hemiparesis, dysarthria); 2) any reversible neurological deficits recognized subjectively and reported by the patients (e.g., numbness); 3) no sign of acute hemorrhage or cerebral infarction in radiological images.

Meanwhile, the total number of symptomatic days was recorded and defined as the duration of postoperative TNEs. According to the previous studies [1], we categorized TNEs into four grades based on the clinical feature and duration of symptoms: Grade 0, no TNE; Grade 1, symptoms resolved within 5 days; Grade 2, symptoms were prolonged for 5–9 days; Grade 3; symptoms were prolonged 10 or more days. The TNE grade was classified one step worse if hemiparesis and/or seizure occurred.

2.6. Statistical analysis

Statistical analysis was carried out using SPSS software (v.23.0; IBM Corp., Chicago, IL, USA). Group data were compared using unpaired *t*-test or $\chi 2$ test as appropriate. A multivariate logistic regression analysis was conducted to test the effects of various parameters on the occurrence of TNEs. A forward stepwise model-building procedure was performed for the parameters using $P < 0.15$ achieved in univariate analysis. The level of significance was set at $P < 0.05$. Odds ratios (ORs) and 95% confidence intervals (CIs) for potential risk factors of TNEs were calculated by multivariate logistic regression analyses. An ordinal regression analysis was conducted to test the effects of various parameters on the severity of TNEs. A forward stepwise model-building procedure was performed for the parameters using $P < 0.15$ achieved in univariate analysis. The level of significance was set at $P < 0.05$. And the Odds ratios (ORs) and 95% confidence intervals (CIs) for potential risk factors of TNE severity were calculated by ordinal regression analyses.

To reduce the imbalance of baseline characteristics between the two groups, Propensity-score analysis were used to compare outcomes of patients with TNEs and without TNEs. Based on covariates from the logistic model, we generated a propensity score for each patient with respect to age, sex, presentation type, frequent TIA or recent infarctions, admission mRS score, Suzuki stage, posterior cerebral artery (PCA) involvement, and surgery side.

3. Results

3.1. Clinical characteristics of patients included in this study

A total of 195 hemispheres in 171 patients were included in this study, 18 other cases with evidence of postoperative infarction shown on MRI were excluded. Among them, there were 14 pediatric patients ($<$ 15 years old) and 157 adult and adolescent patients ($\geq$ 15 years old). Onset symptoms included transient ischemic attack in 67 hemispheres, ischemic stroke in 54, intracranial bleeding in 56, headache in

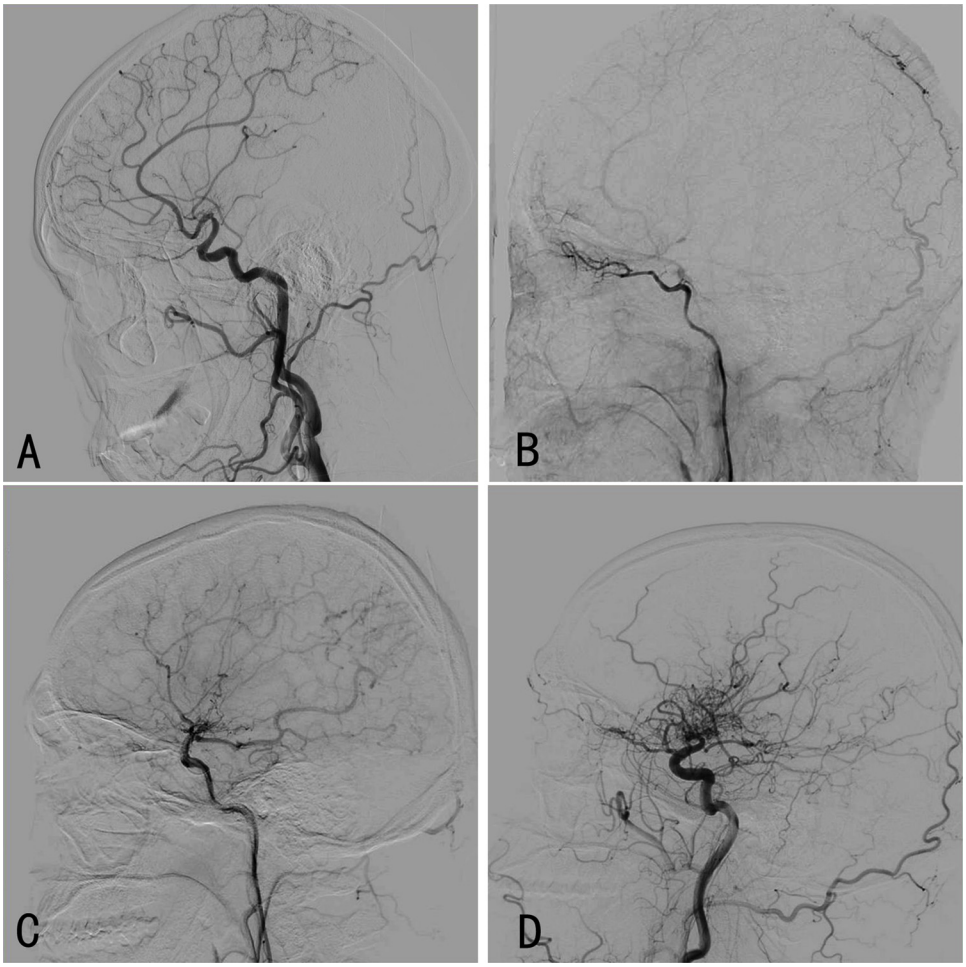

Fig. 1. Representative internal carotid artery angiogram (lateral view) for each moyamoya vessels grade (MMVs): absent (A, B), fair (C), abundant (D).

9, seizure in 7 and asymptomatic in 2. 11 patients had neurological symptoms (Modified Rankin Scale score > 1) at the time of admission. Of the 195 hemispheres, preoperative cerebral infarction and/or frequent preoperative transient ischemic attack (TIA) (more than 2 episodes during the preceding month) during the month preceding surgery was seen in 21 hemispheres. Which indicates the hemodynamic instability of cerebral blood flow in these patients [6,12,39].

The baseline characteristics of patients with postoperative TNEs were also presented in Table 1. Preoperative cerebral lesions were seen in 134 hemispheres including cerebral infarctions in 70 hemispheres and chronic hemorrhagic foci in 64 hemispheres. Most hemispheres exhibited occlusion of the proximal portions of both A_1 and M_1. Stenoocclusive change of the PCA was seen in 64 hemispheres. Preoperative CTP studies revealed decreased cerebral perfusion in all hemispheres. Regarding Suzuki angiographic stages [35], 3 patients were in stage 1, 44 patients were in stage 2, 98 patients were in stage 3, 10 patients were in stage 4, 20 patients were in stage 5 and the remaining 20 patients were in stage 6.

3.2. Incidence and clinical features of TNEs

Intraoperative indocyanine green (ICG)angiography proved bypass patency in all operated hemispheres. Among all treated cases, postoperative TNEs occurred in 40 (20.5%) hemispheres. In adult cases, TNEs was detected in 38 (21.2%) of 179 operated hemispheres, whereas in pediatric cases, TNEs was detected in 2 (12.5%) of 16 operated hemispheres. Symptoms of 40 patients who developed TNEs after surgery varied widely (Table 2): There were 17 (42.5%) aphasia, 9 numbness of the extremities (22.5%), 6 seizures (15%), 5 motor weakness (12.5%), 4 dysarthria (10%) and 6 Hand clumsiness (including facial palsy) (15%). The distribution of TNE grade was as follows; 155 (79.5%) were grade 0, 26 (13.4%) were grade 1, 11 (5.6%) were grade 2, and 3 (1.5%) were grade 3.

The median time TNE occurrence was on postsurgical day 4, and the average duration was 3 ± 2.7 days. Neurological symptoms disappeared within 24 h in 16 (40%) of 40 hemispheres but persisted for 2–12 days in 24 cases (60%), which also disappeared afterward. All TNEs were resolved without any permanent neurologic deficit.

Among 40 hemispheres presented with postoperative TNEs, at the time of discharge, 38 hemispheres had an mRS score of 1 and two had an mRS score of 2. No significant difference regarding mRS score at the time of discharge was found between patients with and without postoperative TNEs ($P > 0.05$). The overall mRS scores of the two groups at admission and discharge were shown in Fig. 2 ($P > 0.05$).

3.3. Independent predictors of TNEs and TNE severity

TNEs occurred more frequently after left-sided surgery than right-sided surgery (24 vs. 16, respectively). Local cortical edematous lesion (Fig. 3) was observed in 19 cases, 13 of which presented with postoperative TNEs.

The correlation of various factors on postoperative TNEs in MMD patients are shown in Table 3. Logistic regression analysis indicated female, left-sided surgery and the presence of the postoperative local cortical edematous lesion as the independent predictors of postoperative TNEs in patients with MMD (OR, 3.0; 95% CI, 1.1–8.2;

Table 1
Baseline characteristics of patients with and without postoperative TNEs.

Characteristics	All Pts (n = 195)	Postop TNEs		p Value
		Present (n = 40)	Absent(n = 155)	
Age, mean ± SD	38.8 ± 13.0	40.2 ± 12.4	38.4 ± 13.3	0.452
Adults	179 (91.8)	38 (92.5)	141 (91.0)	
Children	16 (8.2)	2 (7.5)	14 (9.0)	
Sex				0.083
M	92 (47.2)	14 (35.0)	78 (50.3)	
F	103 (52.8)	26 (65.0)	77 (49.7)	
Presentation				
Ischemic	121 (62.1)	27 (67.5)	94 (60.6)	0.109
Infarction	54 (27.7)	12 (30.0)	42 (39.4)	
TIA	67 (34.4)	15 (37.5)	52 (20.6)	
Hemorrhagic	56 (28.7)	9 (22.5)	47 (30.3)	
Nonspecific	18 (9.2)	4 (10.0)	14 (9.1)	
Headache	9 (4.6)	1 (2.5)	8 (5.2)	
Epilepsy	7 (3.6)	2 (5.0)	5 (3.2)	
Asymptomatic	2 (1.0)	1 (2.5)	1 (0.7)	
Admission mRS score				0.334
1	184 (94.3)	39 (97.5)	145 (93.5)	
2	11 (5.7)	1 (2.5)	10 (6.5)	
Prep condition				
Hypertension				0.553
Suzuki stage†				0.704
1	3 (1.5)	1 (2.5)	2 (1.3)	
2	44 (22.5)	6 (15.0)	38 (24.5)	
3	98 (50.3)	22 (55.0)	76 (49.0)	
4	10 (5.1)	3 (7.5)	7 (3.2)	
5	20 (10.3)	5 (12.5)	17 (11.0)	
6	20 (10.3)	3 (7.5)	17 (11.0)	
MAP pre-surgery	88.7 ± 11.4	92.2 ± 12.0	87.8 ± 11.1	0.029
MAP post-surgery	89.4 ± 10.7	90.8 ± 10.8	89.0 ± 10.8	0.337
Neurological symptoms				0.334
Yes	11 (5.6)	1 (2.5)	10 (6.5)	
No	184 (94.4)	39 (97.5)	145 (93.5)	
Frequent TIA/INF				0.692
Yes	21 (10.8)	5 (12.5)	16 (10.3)	
No	174 (81.2)	35 (87.5)	139 (89.7)	
Preop INF	70 (35.9)	14 (35.0)	56 (36.1)	0.894
Preop ICH	64 (32.8)	9 (22.5)	55 (35.4)	0.119
Preop MRI findings				0.184
No ischemia	51 (26.2)	15 (37.5)	36 (23.2)	
FLAIR changes	131 (67.2)	23 (57.5)	108 (69.7)	
DWI changes	13 (6.6)	2 (5.0)	11 (7.1)	
MMVs				0.467
Absent	18 (9.2)	5 (12.5)	13 (8.4)	
Fair	133 (68.2)	27 (67.5)	106 (68.4)	
Abundant	44 (22.6)	8 (20.0)	36 (23.2)	
ACA depiction				0.313
Good	79 (40.5)	19 (47.5)	60 (38.7)	
Poor	116 (59.5)	21 (52.5)	95 (61.3)	
MCA depiction				0.399
Good	86 (44.1)	20 (50.0)	66 (42.6)	
Poor	109 (55.9)	20 (50.0)	89 (57.4)	
A_1				0.945
Occlusion	150 (76.9)	30 (75.0)	120 (77.4)	
Stenosis	14 (7.2)	3 (7.5)	11(7.0)	
Patent	31 (15.9)	7 (17.5)	24 (15.6)	
M_1				0.671
Occlusion	167 (85.6)	36 (90.0)	131 (84.5)	
Stenosis	20 (10.3)	3 (7.5)	17 (11.0)	
Patent	8 (4.1)	1 (2.5)	7 (4.5)	
PCA involvement				0.237
Yes	64 (32.8)	10 (25.0)	54 (34.8)	
No	131 (67.2)	30 (75.0)	101 (66.2)	
DSA stage				0.261
Early MMD	7 (3.6)	3 (7.5)	4 (2.7)	
IC	87 (44.6)	19 (47.5)	68 (43.8)	
EC	101 (51.8)	18 (45.0)	83 (53.5)	
Surgery side				0.068
Left side surgery	92 (47.2)	24 (60.0)	68 (43.9)	
Right side surgery	103 (52.8)	16 (40.0)	87 (57.1)	
Edematous lesion				< 0.001
Yes	27 (21.5)	17 (42.5)	10 (6.5)	
No	168 (78.5)	23 (57.5)	145 (93.5)	

(*continued on next page*)

Table 1 (*continued*)

Characteristics	All Pts (n = 195)	Postop TNEs		p Value
		Present (n = 40)	Absent(n = 155)	
Discharge mRS score				0.682
1	180 (92.3)	38 (95.0)	142 (91.6)	
2	13 (6.7)	2 (5.0)	11 (7.1)	
3	2 (1.0)	0 (0.0)	2 (1.3)	

pts = patients; ICH = intracerebral hemorrhage; INF = infarction; MMV = moyamoya vessel; IC = intracranial anastomosis rout; EC = extra-intracranial anastomosis rout.
Values are numbers of cases (%) unless otherwise indicated. Mean values are presented with SDs.
† In this and successive tables, Suzuki stage refers to the Suzuki stage of the surgically treated side.

Table 2
Clinical features of TNEs after surgery.

Onset of TNEs, POD, median [range]	4 [0-10]
Duration of TNEs, days, mean ± SD	3.0 ± 2.7
Symptoms included in TNE	
Dysarthria	4(10.0%)
Aphasia	17(42.5%)
Numbness	9(22.5%)
Motor weakness	5(12.5%)
Seizure	6(15.0%)
Other	6(15.0%)
TNE grade	
Grade 0	155 (79.5%)
Grade 1	26 (13.4%)
Grade 2	11 (5.6%)
Grade 3	3 (1.5%)

P = 0.03, OR, 2.9; 95% CI, 1.2–7.0; P = 0.02 and OR, 17.4; 95% CI, 5.7–53.0; P < 0.001).

Likewise, the correlation of various factors on severity of TNE are shown in Table 4. The ordinal regression analysis demonstrated that DSA stage (OR,0.05; 95% CI 0.0-0.5; p = 0.005, OR, 0.08; 95% CI, 0.0-0.4; p = 0.008), PCA involvement (OR, 2.75; 95% CI, 1.0–7.4; p = 0.046), surgery side (OR, 2.73; 95% CI, 1.2–6.5; p = 0.022) and edematous lesion (OR, 21.2; 95% CI, 7.6–59.7; P < 0.001) were significantly associated with TNE severity (Table 4).

4. Discussion

TNEs are frequently observed after revascularization surgery in MMD patients [1,4,9,12,20,26,29]. Although local cortical hyperperfusion [3,4,20], hypoperfusion [29], and watershed shift [12] have been suggested as causes of TNEs; the underlying mechanisms remain unclear. This study demonstrates that TNE occurs in 20.5% of patients with MMD after combined direct and indirect revascularization surgery. In some researches, the incidence of TNEs was significantly higher in adult patients than in pediatric ones [38], but no consensus was reached in our study (P > 0.05). And the average duration of TNE was 3 ± 2.7 days. Majority of the symptoms resolve within 7 days, but in two cases, symptoms persist for 12 days. Our results confirm that female, left-sided surgery and the presence of the postoperative local cortical edematous lesion as the independent predictor of postoperative TNEs in patients with MMD. In addition, there is a strong correlation between left-sided surgery and edematous lesion with TNE grade. Patients with poor collateral pathways are likely to develop a higher grade of TNE. Although the preoperative severity of hemodynamic compromise was not present as a risk factor of postoperative TNEs in our study, it does have a strong relationship with other postoperative complications [6,40]. Therefore, examinations used to evaluate the preoperative severity of hemodynamic compromise were necessary.

As far as we know, this study first demonstrates that female patients were twice more likely to develop postoperative TNEs than male patients. As the incidence of disease progression in MMD is much higher in female patients [23], it somewhat suggests that the cerebral hemodynamic of female patients with MMD is more unstable. Therefore, the potential risk for TNEs in female patients is much higher than

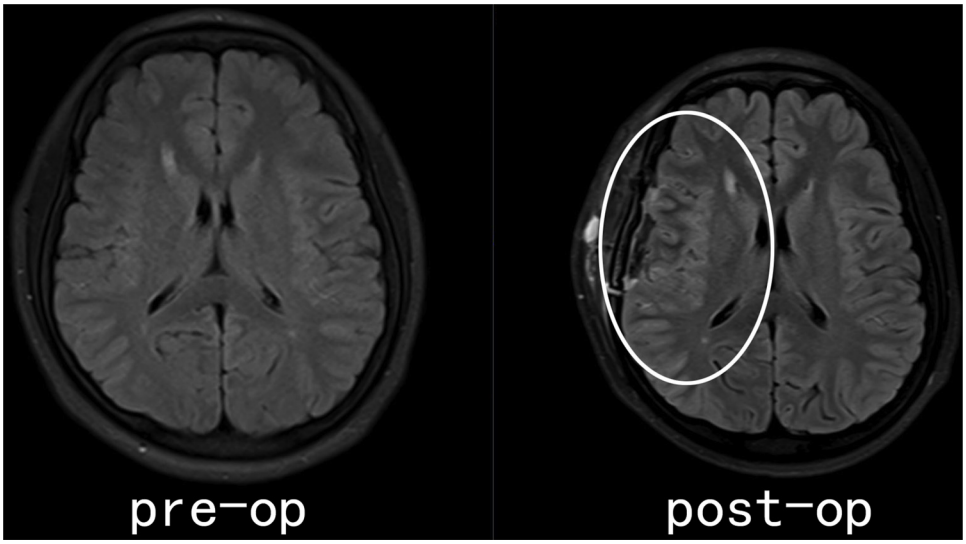

Fig. 2. Comparison of mRS scores of patients at the time of discharge with and without TNEs. The proportions of patients with mRS scores ranging from 1 (grey) to 3 (black) are shown for all patients at discharge (A), patients in the propensity-score matched groups— scores at discharge (B).

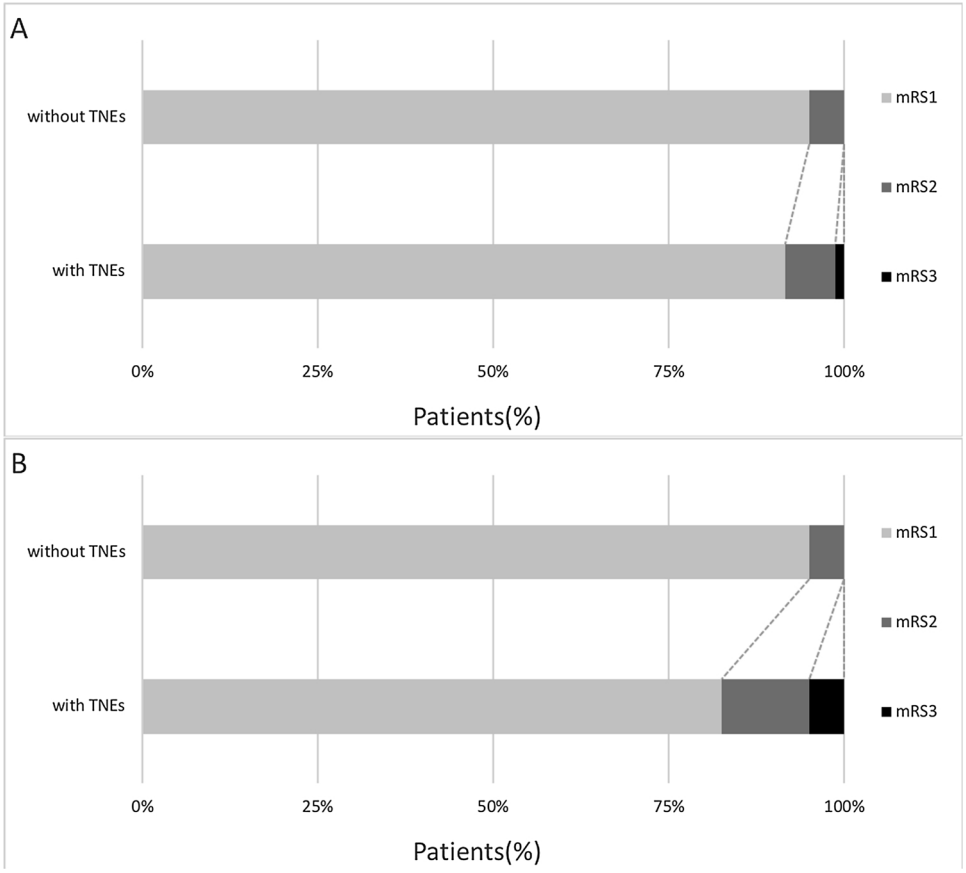

Fig. 3. Representative fluid-attenuated inversion recovery magnetic resonance images of edematous lesion after the combined bypass surgery.

Table 3
Logistic regression analysis for TNEs.

Characteristics	Univariate Analysis	Multivariate Analysis	OR(95% CI)
Age	0.450	0.508	
Female sex	0.086	0.030	3.0 (1.1-8.2)
Ischemic presentation	0.161	0.632	
Suzuki stage (≥4)	0.763	0.332	
MAP pre-surgery	0.032	0.110	
Marked MMVs	0.451	0.698	
Frequent TIA/INF	0.693	0.697	
A_1 occlusion	0.746	0.868	
M_1 occlusion	0.382	0.386	
poor ACA depiction	0.314	0.105	
poor MCA depiction	0.400	0.500	
PCA involvement	0.813	0.078	
DSA stage	0.183	0.224	
Left side surgery	0.071	0.023	2.9 (1.2-7.0)
Edematous lesion	< 0.0001	< 0.0001	17.4 (5.7-53.0)

considered before. The possible reason may be the direct endothelial effects of the estradiol (E2). The vasomotor effect depends on the genomic action of b-estrogen receptors, which activate nitric oxide (NO) synthase and consequently increase NO production, thus modulating vasoreactivity [27,28]. Increased NO production elicits vasodilatation in arteries with a normal endothelium and might attenuate or even abolish it in arteries with endothelial dysfunction [7]. However, vascular reactivity of MMVs was reduced in MMD patients [10,14]. Vasodilatation of the normal vascular territory may induce steal phenomenon, which aggravates the hypoperfusion of the cerebral microcirculation. Therefore, it might be proposed as the causes of female patients with MMD are more likely to develop TNEs after combined bypass surgery.

Our study also demonstrated that TNEs occurred more frequently in patients underwent left-sided surgery (OR, 2.9; 95% CI, 1.2–7.0; P = 0.02) replicates the findings of a prospective study conducted by Uchino et al. [38]. The hemispheric difference might be related to the higher eloquence of the left hemisphere which makes neurological manifestations more obvious. Besides, we also observed that verbal symptom was the most common symptom and tended to have a longer duration than other symptoms (mean duration 4 vs. 2 days, respectively), which suggested that language function may be more sensitive to cerebral blood flow (CBF) changes. As dominant hemispheres usually locate on the left side of the brain, left-sided surgery also aggravates the TNE severity.

As aforementioned, the presence of the postoperative local cortical edematous lesion may contribute to the TNEs as well as the TNE severity. In this study, the edematous lesion was defined as cortical hyperintensity along with subcortical low-intensity on fluid-attenuated inversion recovery (FLAIR) images. Recent studies reveal that the subcortical low-intensity on FLAIR images is due to vasogenic edema [9,26,34]. In MMD patients, chronic ischemia might cause an autoregulatory failure which leading to cerebral arteriolar dilation, breakdown of the blood-brain barrier, and extravasation of the fluid to the brain parenchyma [32]. And it was speculated to be the reason of the vasogenic brain edema. In addition, hemodynamic changes by direct bypass might cause ischemia-reperfusion injury, resulting in overproduction of free radicals, and leading to the presence of subcortical low-intensity [26]. Lee et al. [24] also suggested that free radicals and cytotoxic edema may play roles as a causative factor for subcortical low-intensity. Moreover, the edematous lesion on FLAIR completely disappeared when patients reviewed 3–6 months after surgery in our population. The edematous lesion is completely reversible once the TNE is over. Anyway, this study suggested that both vasogenic and cytotoxic edema can be hypothesized as the pathophysiology of the edematous

Table 4
Relationships between TNE severity and clinical characteristics.

	TNE grade					Ordinal regression analysis	OR
Characteristics	Grade 0	Grade 1	Grade 2	Grade 3	p Value		(95%CI)
Age	38.4 ± 13.3	39.9 ± 12.1	42.7 ± 14.2	32.7 ± 4.6	0.427§	0.392	
Female sex	77 (49.7)	19 (73.1)	6 (54.5)	1 (33.3)	0.121‡	0.065	
Ischemic presentation	94 (60.6)	16 (61.5)	9 (81.8)	2 (66.7)	0.121‡	0.471	
Suzuki stage† (≥4)	41 (26.5)	8 (30.8)	3 (27.3)	0 (0.0)	0.833‡	0.635	
DSA stage					0.204*		
Early MMD	4 (2.7)	1 (3.8)	2 (18.2)	0 (0.0)		Ref	
IC	68 (43.8)	12 (46.2)	6 (54.5)	1 (33.3)		0.005	0.05 (0.0-0.5 s)
EC	83 (53.5)	13 (50.0)	3 (27.3)	2 (66.7)		0.008	0.08 (0.0-0.4)
MAP pre-surgery	87.8 ± 11.1	94.8 ± 11.8	88.5 ± 11.7	82.0 ± 7.2	0.031§	0.701	
Marked MMVs	36 (23.2)	5 (19.2)	2 (18.2)	1 (33.3)	0.687‡	0.216	
Frequent TIA/INF	16 (10.3)	2 (7.7)	2 (18.2)	1 (33.3)	0.581‡	0.269	
A_1 occlusion	120 (77.4)	20 (76.9)	7 (63.6)	3 (100.0)	0.735‡	0.968	
M_1 occlusion	131 (84.5)	24 (92.3)	9 (81.8)	3 (100.0)	0.408‡	0.141	
poor ACA depiction	95 (61.3)	14 (53.8)	5 (45.5)	2 (66.7)	0.311‡	0.274	
poor MCA depiction	89 (57.4)	15 (57.7)	4 (36.4)	1 (33.3)	0.326‡	0.527	
PCA involvement	54 (34.8)	8 (30.8)	1 (9.1)	1 (33.3)	0.204‡	0.046	2.75 (1.0-7.4)
Left side surgery	68 (43.9)	15 (57.7)	6 (54.5)	3 (100.0)	0.061‡	0.022	2.73 (1.2-6.5)
Edematous lesion	10 (6.5)	10 (38.5)	4 (36.4)	3 (100.0)	< 0.001‡	< 0.001	21.2 (7.6-59.7)

INF = infarction; MMV = moyamoya vessel; IC = intracranial anastomosis rout; EC = extra-intracranial anastomosis rout Values are numbers of cases (%) unless otherwise indicated. Mean values are presented with SDs † In this and successive tables, Suzuki stage refers to the Suzuki stage of the surgically treated side. §One-way ANOVA; ‡Mann-Whitney U test; *Kruskal-Wallis H test.

lesion, and it may contribute to the occurrence and severity of TNE in MMD.

Although several authors have discussed the varied clinical features of TNEs and factors that associated with TNE severity, to the best of our knowledge, there was no report about the relationship between clinical characteristics and TNE severity in a large sample. In this study, ordinal regression analysis is used to explore the predictors of TNE severity in MMD patients. As the results show, the DSA stage and PCA involvement were related to the severity of TNE. The DSA stage along with PCA involvement was used to evaluate the compensation of the cerebral perfusion. Due to steno-occlusive changes in PCA and lack of abundant collateral pathways, tolerance of hemodynamic changes of these patients tend to be worse, and it takes more time to back to the stable after revascularization surgery. Previously, Egashira et al. [1] classified cortical arterial network disruption grade which was useful to predict the severity of TNEs after revascularization. We also used the depiction of ACA and MCA to assess cortical arterial network. However, there was no significant relationship between these factors with TNE severity in this study ($P > 0.05$). As a clinically important measurement, DSA is essential in treating MMD. With the two specifics criteria, we can predict the severity of the TNE more effectively and establish an optimal perioperative management to reduce TNEs.

There are some limitations of this study. First, this was a single-center, retrospective study, therefore potential selection bias might not be excluded. Second, in our study we use CTP to evaluate CBF changes during the perioperative period, which was not a quantitative examination, we can only use it to evaluate whether there is a part of misery perfusion and unstable hemodynamic condition rather than assess the cerebral perfusion changes in patients present TNEs quantitatively. Third, the lack of pediatric patients in this study may induce the bias of the results, further research should include more pediatric patients. And a long-term follow up is indispensable to find out the relationship between the outcome with the occurrence of TNEs as well as the severity of TNE. Last, though we find some risk factors of TNEs and TNE severity, the treatment strategies for TNEs were not standardized in our study population. Further researches are needed to establish a standardized treatment protocol for MMD patients with TNEs after revascularization surgery.

5. Conclusion

TNEs are common postoperative complications after revascularization surgery and certain clinical characteristics might affect the incidence and severity of TNEs. Neurosurgeons should be aware of the risk factors for TNEs, which could prove useful in identifying patients at high risk of TNEs and modifying patients care to minimize the risk of TNEs.

Our study demonstrates that TNEs occurred in 20.5% of the patients with MMD after combined direct and indirect revascularization procedures. We found that edematous lesions and left-sided surgery were independent risk factors for TNEs as well as the severity of TNE. In addition, a pronounced edematous lesion can be a predictor of TNEs. And the PCA involvement and DSA stage can efficiently stratify the clinical severity in MMD patients. The occurrence and severity of TNEs have no relationship with the outcomes during the perioperative period. Whether the TNEs or the severity of TNE are significantly associated with further outcomes need a long-term follow up data to detect.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Funding

This study was funded by the Ministry of Science and Technology of China, National Key Technology Research and Development Program (2015BAI12B04); Beijing Institute for Brain Disorders grant (BIBD-PXM2013_014226_07_000084); and National Natural Science Foundation of China (H0906 81771234to Y.L. Zhao).

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Acknowledgments

We would like to thank the colleagues of Peking University International Hospital and Beijing Tiantan Hospital for their excellent assistance.

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