Hemorrhagic Stroke and the Japan Adult Moyamoya Trial

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Takeshi Funaki, Jun C. Takahashi, Susumu Miyamoto, and the JAM Trial Group

Abstract

The Japan Adult Moyamoya (JAM) Trial was a unique randomized controlled trial demonstrating the effectiveness of direct bypass surgery for hemorrhagic moyamoya disease. Prespecified subgroup analysis undertaken as part of the trial demonstrated that posterior-dominant initial hemorrhage is a significant predictor of rebleeding and an effect modifier for surgery. Periventricular anastomosis—fragile collaterals formed by the lenticulostriate arteries, thalamic perforators, and choroidal arteries—might present a clue to the mechanism of high rebleeding risk linked to posterior hemorrhage. Angiographic analyses of the JAM Trial revealed that choroidal collaterals and the involvement of the posterior cerebral artery are associated with posterior hemorrhage, and subsequent cohort analysis of the nonsurgical group has revealed that choroidal anastomosis is a strong predictor of rebleeding. A better understanding of periventricular anastomosis might contribute to further progress in the surgical treatment of hemorrhagic moyamoya disease.

Keywords

Moyamoya disease · Intracranial hemorrhage · Cerebral revascularization · Periventricular anastomosis · The Japan Adult Moyamoya Trial

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9.1 Introduction

The Japan Adult Moyamoya (JAM) Trial is the only Randomized Controlled Trial (RCT) for moyamoya disease. The trial revealed the effectiveness of direct bypass in preventing rebleeding in adult hemorrhagic moyamoya disease. In this chapter, the authors discuss the mechanism and treatment of hemorrhagic moyamoya disease with a focus on the results of the JAM Trial (see also Chap. 13).

9.2 The JAM Trial

The rebleeding rate of hemorrhagic moyamoya disease can be as high as 7% per year, and the outcome after rebleeding is poor [1]. The rupturing of the fragile collateral vessels typical of the disease, the so-called moyamoya vessels, has been considered the mechanism of hemorrhage in moyamoya disease. The diminishing of such collateral vessels after bypass surgery is well known [2]. This recognition has given rise to the hypothesis that bypass surgery can prevent rebleeding by reducing the hemodynamic burden on the fragile collateral vessels typical of the disease. This hypothesis, however, had remained untested before the JAM Trial.

The JAM Trial was a multicentered RCT, the purpose of which was to test the above hypothesis [3, 4]. The inclusion criteria of the trial are shown in Table 9.1. At the beginning of the study, the optimal sample size was calculated on the assumption that the incidence of adverse neurological events was 8%/y in the nonsurgical group and 4%/y in the surgical group. The follow-up period was 5 years, and the sample size of 160 (80 patients per group) was expected to provide 80% of the statistical validity required to detect a difference between the two groups with a significance level of 0.05. However, this number was reduced to 80 in January 2006 when a far smaller number of patients were discovered to be eligible for the study, as indicated later [3]. Despite the change in sample size, the trial required 12 years to complete.

In the randomization process, the participants were classified as exhibiting either anterior or posterior hemorrhage: the former was defined as hemorrhage occurring in the putamen, caudate, or anterior half of the body of the lateral ventricle; the latter was defined as hemorrhage occurring in the thalamus, the posterior half of the body of the lateral ventricle, or the atrium. Accordingly, each participant was randomly assigned to either the surgical or the nonsurgical group. The JAM Trial Group adopted stratified randomization, which balanced the proportion of anterior and posterior hemorrhage patients assigned to each category, as it had been hypothesized that the surgical effects and rebleeding risk might vary between those with anterior hemorrhage and those with posterior hemorrhage.

The patients assigned to the surgical group underwent direct bypass, superficial temporal artery (STA) to middle cerebral artery (MCA) anastomosis, performed by registered neurosurgeons in different sessions for each side. Neither indirect bypass alone nor high-flow bypass using venous or radial artery graft was permitted. The

Table 9.1 Patient eligibility of the Japan Adult Moyamoya Trial, reprinted from the Japan Adult Moyamoya Trial Group (Neurol Med Chir 44:218–219, 2004)

1. Clinical requirements
(1) Age: Between 18 and 60 years at the time of the initial bleeding episode
(2) Independent in daily life (modified Rankin disability scale 0–2)
(3) Intracranial hemorrhage, intraventricular hemorrhage, or subarachnoid hemorrhage within the preceding 12 months
(4) At least one month has passed after the last stroke episode, either ischemic or hemorrhagic
(5) At least one month has passed after the completion of acute phase treatment for the hemorrhage and for the related secondary pathophysiology (e.g., hydrocephalus)
2. Radiological requirements
(1) Computed tomography/magnetic resonance imaging
(a) Absence of extensive infarction spreading widely over the territory of a main arterial trunk
(b) Absence of contrast enhancement in the infarcted area
(2) Angiography
Angiographic findings should satisfy the diagnostic criteria of the spontaneous occlusion of the circle of Willis (moyamoya disease) published by the Ministry of Health, Labor and Welfare of Japan:
(a) Occlusive lesions are present in the terminal portion of the intracranial internal carotid artery, or in the proximal portion of the anterior or middle cerebral arteries.
(b) Abnormal vascular network demonstrated in the region of basal ganglia and thalamus (moyamoya vessels) in the arterial phase
(c) These findings are present bilaterally
3. Exclusion criteria
(1) Not independent in daily life (modified Rankin disability 3–5)
(2) Atherosclerotic carotid disease, or cardiac arrhythmia which may cause thromboembolic complications
(3) Malignant tumors or organ failure of the heart, liver, kidney, or lung
(4) Unstable angina or myocardial infarction within the past 6 months
(5) Hematological abnormality showing bleeding diathesis
(6) Uncontrolled diabetes with a serum fasting blood glucose level of more than 300 mg/dl, or requiring insulin
(7) Hypertension with a diastolic blood pressure of more than 110 mmHg
(8) Treated by extracranial–intracranial bypass surgery before enrollment
(9) Pregnancy

*The Japan Adult Moyamoya Trial Group thereafter amended the inclusion criteria on age as that between 18 and 65 years

primary endpoint was defined as all adverse events, and the secondary endpoint was a rebleeding attack. All participants were followed for 5 years by a team comprising a particular neurologist and neurosurgeon.

9.3 Primary Results of the JAM Trial

A total of 80 participants, comprising 42 surgical and 38 nonsurgical patients, were eventually enrolled in the trial. All patients completed the 5-year follow-up, and no crossover or failure to follow-up occurred. Kaplan–Meier method revealed that the

incidence of both endpoints was significantly lower in the surgical group than in the nonsurgical group (primary endpoint, $P = 0.048$; secondary endpoint, $P = 0.042$; Fig. 9.1). The rebleeding rate calculated according to the person-year method was 7.6% per year in the nonsurgical group versus 2.7% per year in the surgical group. The hazard ratio (HR) of the secondary endpoint estimated with the Cox proportional hazard model was 0.355, indicating that the rebleeding rate had decreased by two-thirds. On the other hand, the upper limit of 95% confidence interval of the HR slightly exceeded 1, and the primary report of the JAM Trial published in *Stroke* characterized the results as "statistically marginal." The discrepancy in statistical significance between the Kaplan–Meier method and Cox proportional hazard model is apparently attributable to the problem of sample size mentioned above. Conducting an RCT with a larger sample size, however, seems unfeasible considering the difficulty of participant recruitment for the JAM Trial. It should be noted that the primary report of the JAM Trial was accepted by *Stroke* in 2014 with the following

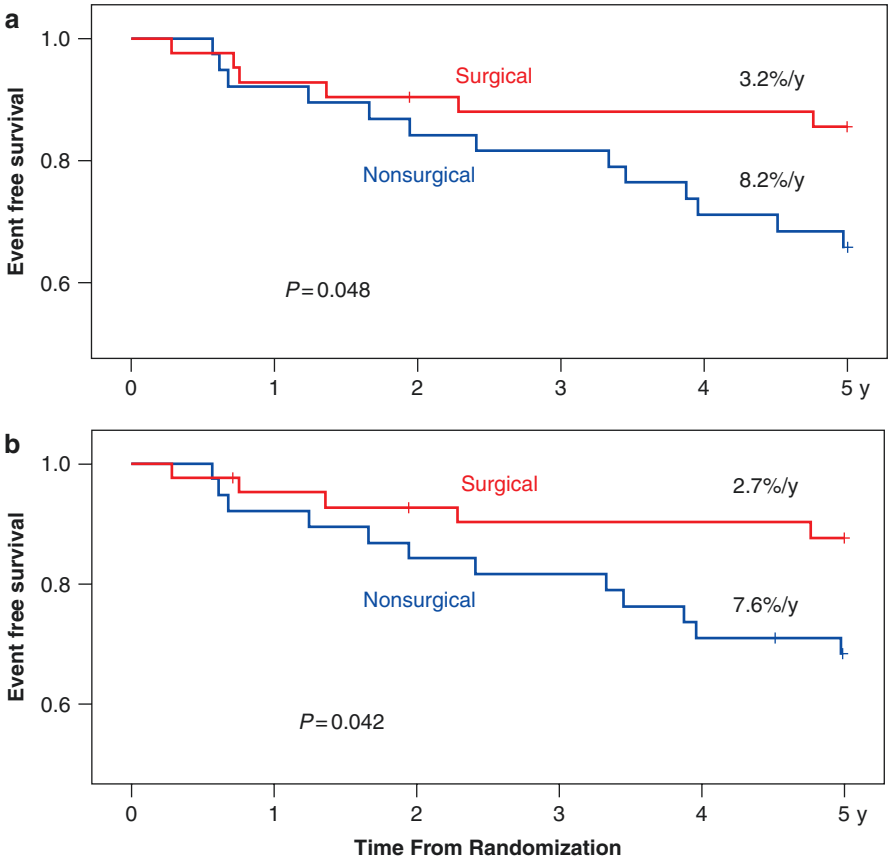

Fig. 9.1 Kaplan–Meier curves for the primary (**a**) and secondary (**b**) endpoints, modified with permission from Miyamoto et al. (*Nippon Rinsho* 2014;72; supple 7: 639–42 [Japanese])

conclusion: *Kaplan–Meier analysis revealed the significant difference between the surgical and nonsurgical group, suggesting the preventive effect of direct bypass against rebleeding* [3].

9.4 Prespecified Subgroup Analysis of the JAM Trial

The JAM Trial Group then investigated the prespecified question of whether the surgical effects and natural course varied with the hemorrhage site at onset, which had been the rationale for the stratified randomization. First, a subgroup analysis by hemorrhage site was performed for all 80 patients. As shown in Fig. 9.2, the HR for the surgical group relative to the nonsurgical group was very low (0.07) in the posterior hemorrhage group, suggesting a high degree of surgical effectiveness, whereas the HR exceeded 1 (1.62) in the anterior hemorrhage group. The test for interaction revealed that the surgical effects varied significantly with the hemorrhage site ($P = 0.013$).

The JAM Trial Group then limited the analysis to the nonsurgical group, which comprised 38 patients, including 21 exhibiting anterior hemorrhage and 17 exhibiting posterior hemorrhage. As shown in Fig. 9.3, the incidence rates for the primary end points were significantly higher for the posterior group than for the anterior group ($P = 0.003$). This indicates that the natural outcome also varied with the hemorrhage site.

These results suggest that patients with posterior hemorrhage have a poorer natural prognosis and accrue greater benefit from surgery. Direct bypass should be considered especially for the posterior hemorrhage group. These results were published

Stratified Variable		Nonsurgical (n=38)	Surgical (n=42)	Hazard Ratio 0.01 0.1 1 10	P Interaction
Hemorrhage site	Anterior	3/21	5/24		0.013
	Posterior	10/17	1/18		
Age	≥42y	6/17	4/22		0.705
	<42y	7/21	2/20		
Sex	Female	10/27	4/28		0.729
	Male	3/11	2/14		
Hypertension	Yes	4/8	2/8		0.377
	No	9/30	4/34		
ICH w/o IVH	Yes	3/8	2/14		0.831
	No	30/10	4/28		

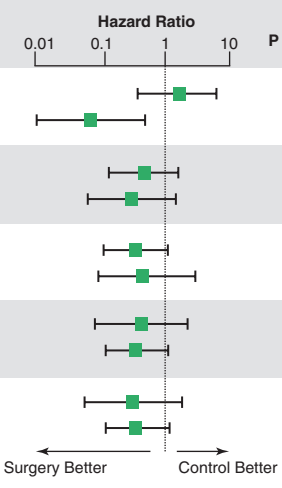

Fig. 9.2 Forest plot showing results of the prespecified subgroup analysis in the Japan Adult Moyamoya Trial, reprinted with permission from Funaki et al. (*Clin Neurosci* 2016;34:1218–1221 [Japanese])

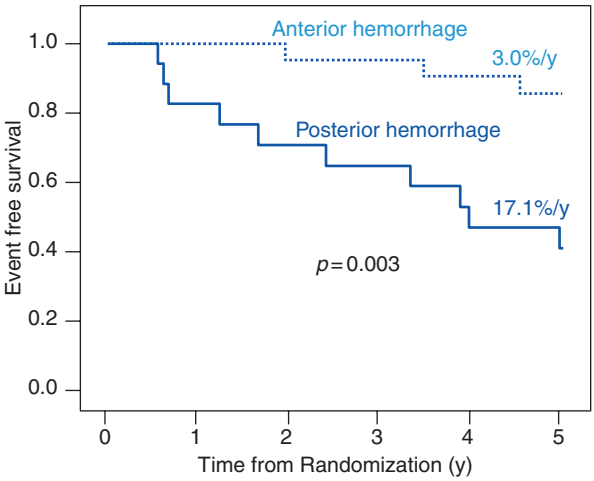

Fig. 9.3 Kaplan–Meier curves for the nonsurgical group in the Japan Adult Moyamoya Trial, reprinted with permission from Funaki e al (*Clin Neurosci* 34:1218–1221, 2016 [Japanese])

in *Stroke* in 2016 [5]. It should be noted that these results are not the product of post hoc analyses; they were obtained from "prespecified" analysis to test the predescribed hypothesis under stratified randomization.

9.5 Mechanism of Bleeding in Moyamoya Disease: Periventricular Anastomosis

The results of the subgroup analysis in the JAM Trial raise new questions about the higher risk of rebleeding evident in patients exhibiting posterior hemorrhage. Answering this question requires an understanding of the fragile collateral vessels typically associated with the disease. The issue of hemorrhage site can eventually be traced to the fragile collateral vessels responsible for bleeding (see also Chap. 13).

Hemorrhage in moyamoya disease occurs in various sites of the cerebrum, including the basal ganglia, thalamus, subcortical area, subependymal area, and ventricle [6]. The wide distribution of potential hemorrhage sites can be explained by the presence of the various abnormal collateral vessels that cause the hemorrhage. Although researchers had considered so-called "basal moyamoya vessels" as the vessels responsible for bleeding, some of the hemorrhages occurring in moyamoya disease cannot be traced to the basal moyamoya vessels comprising the lenticulostriate arteries.

In 2003, Morioka et al. reported that abnormal dilatation and extension of the anterior choroidal artery or the perforator from the posterior communicating artery were more commonly observed in hemorrhagic moyamoya disease than in the ischemic form of the disease [7]. This finding suggests that not only lenticulostriate arteries but also thalamic perforators and choroidal arteries are associated with hemorrhage in moyamoya disease. A recent study using high-resolution black-blood

MRA has demonstrated that all three arteries—lenticulostriate, thalamic perforating, and choroidal—share the common feature of serving as collaterals to the cortex [8]. These arteries anastomose to the medial end of the medullary or insular arteries, which supply blood from the cortex to the cerebral depths in normal anatomy. As a result of this change, the direction of blood flow in the medullary artery is reversed to supply blood from the depths to the cortex. This type of collateral system, typical of moyamoya disease, has been referred to as "periventricular anastomosis" (Fig. 9.4) [8, 9].

The formation of periventricular anastomosis is explained by the theory of ventriculofugal and ventriculopetal arteries [10]. According to this famous theory advocated by Van den Bergh in 1969, the deep white matter is supplied by two arterial systems: the ventriculopetal artery (i.e., medullary artery) from the surface to the ventricle; and the ventriculofugal artery form the ventricle to the surface (Fig. 9.5). The ventriculofugal artery, also known as the subependymal artery [11], is formed by the peripheral ends of the perforating or choroidal arteries [12].

The ventriculofugal and ventriculopetal arteries form no anastomosis in normal anatomy, as the border zone between these arteries is believed to be the cause of periventricular ischemia. In moyamoya disease, a long-standing cortical ischemia might induce an abnormal connection between these arteries and result in periventricular anastomosis. In the early 1970s, Kodama et al. suggested the possibility of such a connection forming between perforating and medullary arteries [13].

The results of recent studies shed light on the significance of periventricular anastomosis as a hemorrhage-prone collateral in moyamoya disease [8, 14–16]. Anastomotic sites in the periventricular collaterals are considered especially fragile because of the histopathological connection between vessels. Even microaneurysms frequently emerge at the sites of anastomoses because of the characteristic inflection points that typically form in the collaterals at these sites.

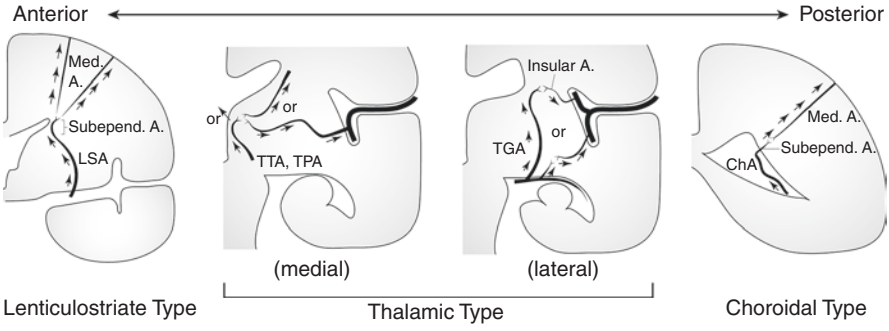

Fig. 9.4 Schematic illustration showing a coronal plane of the left hemisphere and three types of periventricular anastomosis, reprinted with permission from Funaki et al. (*Neurol Med Chir (Tokyo)* 2015;55(3):204–9)

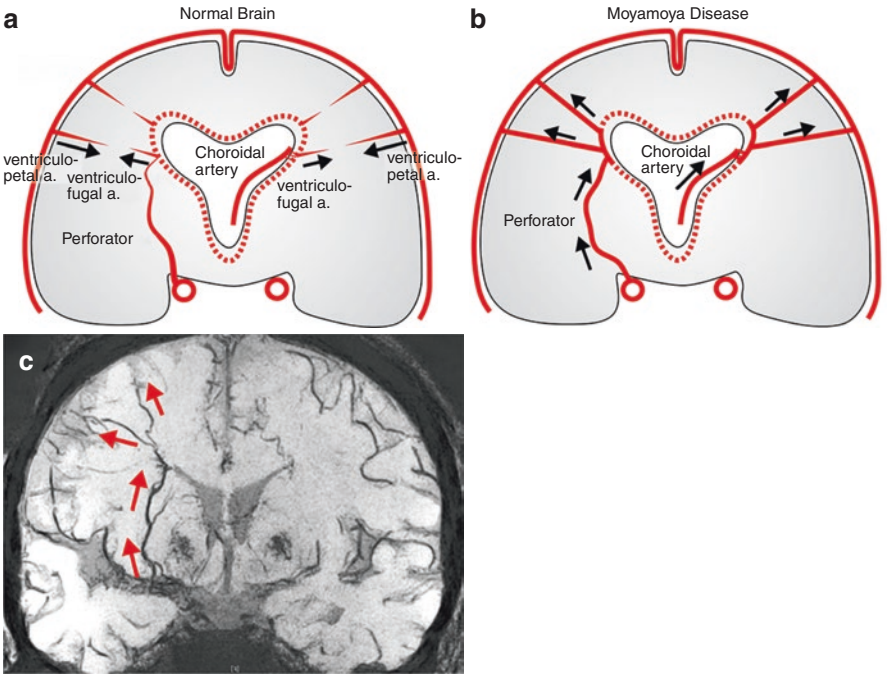

Fig. 9.5 (**a, b**) Schematic illustration showing ventriculopetal/ventriculofugal arterial system on a coronal plane for the normal brain (**a**) and moyamoya disease (**b**) (**c**) Flow-sensitive black-blood MR angiography showing lenticulostriate-type periventricular anastomosis, reprinted with permission from Funaki et al. (Jpn J Neurosurg 2017;26:4–11 [Japanese])

9.6 Why Does the Posterior Hemorrhage Group Have a Poor Natural Prognosis?

The JAM Trial Group performed additional analyses to answer the question of why patients exhibiting posterior hemorrhage are at higher risk of rebleeding. In this analysis, angiographic findings of abnormal collaterals causing hemorrhage were classified into three types—lenticulostriate, thalamic, and choroidal anastomoses—according to the theory of periventricular anastomosis (Fig. 9.6) [15].

Lenticulostriate anastomosis. A positive angiographic indicator of lenticulostriate anastomosis is extreme dilatation and extension of the lenticulostriate arteries with at least one artery extending beyond the level of the pericallosal artery in the lateral view. In such situations, the lenticulostriate arteries are reasonably considered to extend beyond the upper level of the lateral ventricle to connect to the medullary arteries.

Thalamic anastomosis. A positive angiographic indicator of thalamic anastomosis is extreme dilatation and extension of the thalamic perforators with at least one perforator extending beyond the position of the medial posterior choroidal artery in the lateral view. In such a situation, the thalamic perforators are reasonably considered to extend beyond the thalamus to connect to the medullary arteries.

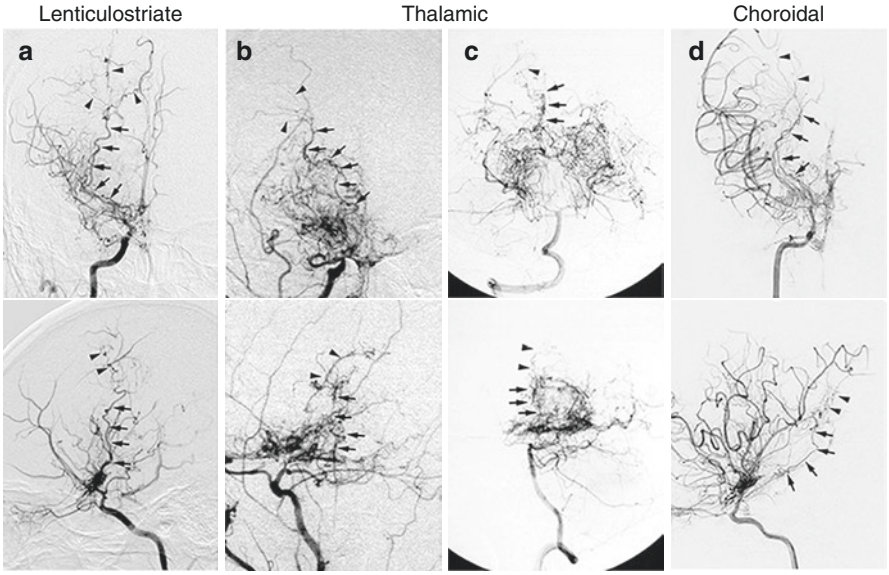

Fig. 9.6 Angiographic definition of collaterals in Japan Adult Moyamoya Trial. (**a**) Lenticulostriate anastomosis. (**b, c**) Thalamic anastomosis. (**d**) Choroidal anastomosis. Anterior–posterior and lateral views are shown in the upper and lower row, respectively. (**a**, **b**), and (**d**) are right carotid angiography; (**c**) is right vertebral angiography. The perforating or choroidal arteries are shown as arrows, the medullary arteries as arrowheads, reprinted with permission from Funaki et al. (Jpn J Neurosurg 2017;26:4–11 [Japanese])

Choroidal anastomosis. This is defined as an anastomosis between the choroidal artery and the medial end of the medullary artery. Both the anterior and the lateral posterior choroidal arteries can serve as the origin of such an anastomosis. Positive angiographic (lateral view) indicators of choroidal anastomosis are as follows: (1) extreme dilatation and extension of the choroidal artery with a sharp deviation of the lateral ventricle at its peripheral portion to connect to the medullary artery; (2) extreme extension of the anterior choroidal or lateral posterior choroidal artery beyond the atrium of the lateral ventricle to the body of the lateral ventricle; or (3) extension of the medial posterior choroidal artery penetrating the corpus callosum to the pericallosal artery.

Analysis of the 75 hemorrhagic hemispheres in the JAM Trial revealed that choroidal anastomosis and involvement of the posterior cerebral artery (PCA) were the significant characteristics of posterior hemorrhage [15]. Choroidal anastomosis typically forms around the atrium and is located in the most posterior of the collaterals [9]. This suggests that the high rebleeding risk of posterior hemorrhage is attributable to the extreme fragility of a choroidal anastomosis distributed posteriorly.

This hypothesis was tested with two additional analyses of the JAM Trial [14, 16]. First, an ancillary study using the 5-year follow-up data on the nonsurgical cohort of the JAM Trial revealed that the presence of choroidal anastomosis is an independent predictor of rebleeding [14]. The adjusted HR for rebleeding in the

choroidal-positive group relative to the negative group was 11.10 (95% confidence interval, 1.37–89.91), suggesting that rebleeding risk is more than ten times higher in the choroidal-positive group than in the negative group. This finding is notable considering that the significance of choroidal anastomosis was first demonstrated in the longitudinal analysis. Second, a case control study compared the data set of the JAM Trial with the angiographic data of adult patients with ischemic-onset moyamoya disease [16]. This analysis revealed that the characteristic pattern of abnormal vascular networks at the base of the brain differ in the ischemic- and hemorrhagic-onset types, with the latter patients showing a significantly higher proportion of thalamic and choroidal anastomoses than the former.

9.7 The Mechanism of Bypass Surgery in Preventing Hemorrhage

The diminishing of the numerous abnormal vessels typical of moyamoya disease following surgery is a well-known postsurgical phenomenon. This can reasonably be explained by the mechanism of periventricular anastomosis. Our data reveal that retrograde flow in the medullary artery can be restored to normal (from surface to depth) after surgery, resulting in elimination of the pathological anastomosis and normalization of the perforating or choroidal arteries [17]. Accordingly, this change might be observed as shrinkage of the abnormal vessels because normograde flow in the medullary artery is almost invisible.

Such a change, which can be viewed as a *normalization* of periventricular vasculature, is considered a key mechanism of bypass surgery in preventing rebleeding, as suggested from the JAM Trial. In other words, a bypass whose perfusion overlaps the cortical distribution of the periventricular anastomosis can normalize the outflow of the medullary artery, resulting in successful shrinkage of the periventricular anastomosis.

According to our additional data of interest, among the three subtypes of periventricular anastomosis, choroidal anastomosis was the type most likely to normalize following bypass surgery [17]. This result corresponds well with the results of prespecified subgroup analysis in the JAM Trial, which suggests the posterior hemorrhage group accrues greater benefit from bypass surgery [5] because choroidal anastomosis is considered a typical bleeding source in posterior hemorrhage. The variance in the likelihood of normalization might be attributable to the differing cortical distribution patterns seen in the subtypes of periventricular anastomosis. Our most recent study revealed that choroidal anastomosis outflows were to the lateral cortex predominantly posterior to the central sulcus, whereas outflows of the lenticulostriate anastomosis were more likely to be characterized as medial and anterior [18].

The knowledge of periventricular anastomosis might promote a new direct-bypass strategy focusing on hemorrhage prevention, which targets the responsible periventricular anastomosis (Fig. 9.7) [19].

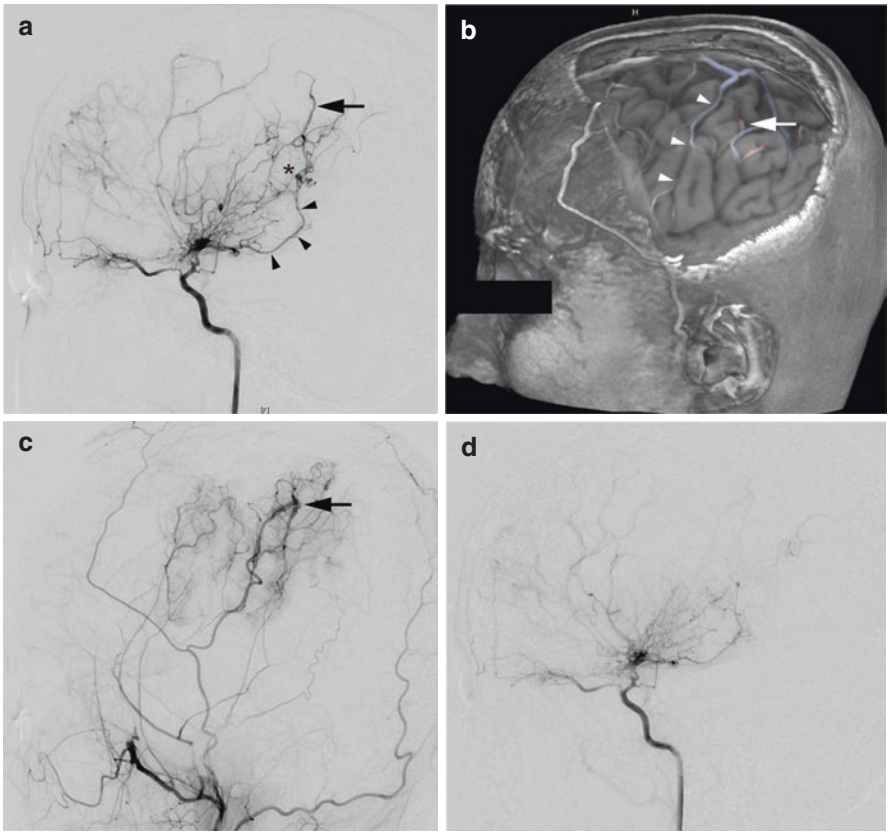

Fig. 9.7 (**a**) Lateral view angiography of the left internal carotid artery before surgery revealing choroidal anastomosis (black arrowheads), extending to the target vessel (arrow). Note the aneurysm observed at the site of the anastomosis (asterisk). (**b**) Corresponding brain surface image generated with MR angiography data. White arrowheads indicate the central sulcus. The target vessel is exposed on the postcentral gyrus (arrow). (**c**) Lateral view angiography of the left external carotid artery obtained 9 months after surgery revealing patency of the bypass and accurate anastomosis to the target vessel (arrow). (**d**) Lateral view angiography of the left internal carotid artery obtained 9 months after surgery revealing marked shrinkage of the choroidal anastomosis and aneurysm, reprinted with permission from Funaki et al. (Neurol Med Chir (Tokyo). 2019;59(12):517–22)

9.8 Additional Sub-analyses of the JAM Trial

Analysis of the nonhemorrhagic hemispheres included in the JAM Trial suggests that choroidal anastomosis is also a predictor of de novo hemorrhage [20]. The annual risk of de novo hemorrhage in the nonhemorrhagic hemispheres was relatively high (5.8% per year). Given that the nonhemorrhagic hemisphere in hemorrhagic moyamoya disease resembles a nonhemorrhagic hemisphere in asymptomatic or less-symptomatic patients, choroidal anastomosis might also be a predictor of de novo hemorrhage in asymptomatic individuals in these populations.

The last analysis of the JAM Trial focused on subgroup analysis by baseline hemodynamic failure [21]. This analysis revealed that hemodynamic failure is an independent risk factor for subsequent hemorrhage in hemorrhagic moyamoya disease. Moreover, the analysis revealed that the subgroup exhibiting hemodynamic failure tended to accrue greater benefit from surgery; however, the test for interaction was not statistically significant ($P = 0.056$) [21].

9.9 Summary

The results of the JAM Trial are dramatically changing the treatment of hemorrhagic moyamoya disease. The recent findings on choroidal anastomosis might also overturn the conventional understanding of the mechanism of hemorrhage that focuses solely on the "basal moyamoya vessels." Such a paradigm shift might promote further progress in the surgical treatment of hemorrhagic moyamoya disease.

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