JNS

CLINICAL ARTICLE

Effect of choroidal collateral vessels on de novo hemorrhage in moyamoya disease: analysis of nonhemorrhagic hemispheres in the Japan Adult Moyamoya Trial

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OBJECTIVE Following hemorrhagic stroke in moyamoya disease, de novo intracranial hemorrhage can occur in the previously unaffected nonhemorrhagic hemisphere. In the present analysis the authors intended to determine whether the presence in the nonhemorrhagic hemisphere of choroidal collateral vessels, which have been the focus of attention as a source of bleeding, affects the risk of de novo hemorrhage.

METHODS The subject of focus of the present cohort study was the nonhemorrhagic hemispheres of adult patients with hemorrhagic moyamoya disease enrolled in the Japan Adult Moyamoya Trial and allocated to the nonsurgical arm. The variable of interest was the presence of choroidal collaterals (also termed choroidal anastomoses), identified with baseline angiography and represented by a connection (anastomosis) between the anterior or posterior choroidal arteries and the medullary arteries. The outcome measure was de novo hemorrhage during the 5-year follow-up period, assessed in all nonhemorrhagic hemispheres. The incidence of de novo hemorrhage in the collateral-positive and -negative groups was compared.

RESULTS Choroidal collaterals were present in 15 of 36 (41.7%) nonhemorrhagic hemispheres analyzed. The overall annual risk of de novo hemorrhage was 2.0%. Three de novo hemorrhages occurred in the collateral-positive group, whereas no hemorrhage occurred in the collateral-negative group. The annual risk of de novo hemorrhage was significantly higher in the collateral-positive group than in the collateral-negative group (5.8% per year vs 0% per year; p = 0.017). All hemorrhage sites corresponded to the distribution of choroidal collaterals.

CONCLUSIONS The present preliminary results suggest that the presence of choroidal collaterals affects the risk of de novo hemorrhage in the nonhemorrhagic hemisphere, subject to verification in larger studies. Further studies are needed to determine the optimal treatment strategy for nonhemorrhagic hemispheres and asymptomatic patients.

https://thejns.org/doi/abs/10.3171/2018.10.JNS181139

KEYWORDS moyamoya disease; intracranial hemorrhage; choroidal artery; cohort studies; nonhemorrhagic hemisphere; vascular disorders

Moyamoya disease is characterized as chronic progressive stenosis of the terminal portion of the bilateral internal carotid arteries and the formation of various fragile collaterals typical of the disease.[16] Hemorrhagic moyamoya disease is a type of disease manifesting intracranial hemorrhage due to rupture of fragile collaterals. Recurrent bleeding is a major concern in hemorrhagic moyamoya disease; the incidence is as high as 7% per year.[9,12] Patients can suffer rebleeding even in the previously unaffected hemisphere. Such contralateral

ABBREVIATIONS JAM = Japan Adult Moyamoya; PCA = posterior cerebral artery; TIA = transient ischemic attack.

SUBMITTED April 26, 2018. **ACCEPTED** October 15, 2018.
INCLUDE WHEN CITING Published online February 8, 2019; DOI: 10.3171/2018.10.JNS181139.

bleeding is a unique phenomenon in that the unaffected nonhemorrhagic hemisphere subsequently suffers de novo hemorrhage. De novo hemorrhage in the nonhemorrhagic hemisphere is not rare, although it is less frequent than rebleeding in the hemorrhagic hemisphere.[8,11]

Focusing on the nonhemorrhagic hemisphere has clinical significance in two respects: First, it might provide valuable information for a surgeon deciding whether to perform extracranial-intracranial bypass to prevent hemorrhage[12] in the nonhemorrhagic hemisphere; second, it might suggest optimal management for asymptomatic moyamoya disease, which leads to devastating de novo hemorrhage in a certain proportion of sufferers.[10]

An earlier analysis from the Japan Adult Moyamoya (JAM) Trial revealed that the choroidal collateral (also termed the choroidal anastomosis), a fragile collateral vessel characterized as a connection (anastomosis) between the choroidal and medullary arteries, was a predictor for rebleeding in hemorrhagic moyamoya disease.[5] This result reasonably leads to the hypothesis, previously untested, that the presence of choroidal collaterals is also a predictor for de novo hemorrhage in the nonhemorrhagic hemisphere.

The purpose of the present analysis of hemorrhagic moyamoya disease was to estimate the incidence of de novo hemorrhage in the nonhemorrhagic hemisphere and to determine whether the presence of choroidal collateral vessels affects the risk of hemorrhage.

Methods

Study Design

This study is an ancillary cohort study using longitudinal data on the nonhemorrhagic hemispheres treated conservatively in the JAM Trial and was approved by the ethics committees of all participating centers.

The JAM Trial (registered with the University Hospital Medical Information Network Clinical Trials Registry, clinical trial registration no.: C000000166 [www.umin.ac.jp/ctr/index.htm], 2005) was originally designed as a multicenter randomized controlled trial to test the hypothesis that extracranial-intracranial bypass was beneficial for hemorrhagic moyamoya disease. The patient inclusion criteria were as follows: diagnosis of moyamoya disease according to the guidelines proposed by the Ministry of Health and Welfare of Japan;[3] intracranial hemorrhage within 12 months; age 16 to 65 years; independent in daily life (0 to 2 for modified Rankin Scale score); completion of acute-phase treatment at least 1 month prior to study entry; and free from ischemic/hemorrhagic attack for at least 1 month.[12] All participants had bilateral carotid lesions, as patients demonstrating solely unilateral lesions were excluded. Participants were randomly allocated to either surgical or nonsurgical treatment. For each patient in the surgical group, staged bilateral surgery (superficial temporal artery–middle cerebral artery anastomoses) was performed. Patients allocated to the nonsurgical group received the best medical treatment. As stated in our first report,[12] blood pressure medication was given to patients with hypertension to control it, and the use of anticoagulants or antiplatelet drugs was not allowed unless the patient was having significant cerebral ischemic attacks. Both groups were followed for 5 years by neurologists and neurosurgeons.

Study Subjects

For the present study the focus of investigation was the nonhemorrhagic hemispheres of patients included in the JAM Trial, and data regarding these hemispheres in particular were extracted from the patient data of the nonsurgical group. As reported previously,[4] an imaging board categorized the hemisphere in which the initial hemorrhage occurred just before enrollment as either right or left for each patient according to the findings on CT studies (and MRI studies if available). The nonhemorrhagic hemispheres were also identified by this process. Patients whose nonhemorrhagic hemisphere could not be determined for some reason were excluded from the analysis. Nonhemorrhagic hemispheres with a history of hemorrhagic stroke prior to the trial were also excluded.

Variables

The imaging board—all members of which were blinded from clinical information, including the hemispheres involving the initial and subsequent hemorrhages—used baseline angiography to measure and grade the angiographic parameters outlined below. This measurement was performed after completion of patient follow-up and separately from the determination of the hemorrhagic hemisphere.

The angiographic definition of choroidal collateral (choroidal anastomosis), a primary variable of interest, has been presented in detail elsewhere.[4,5] In brief, it is defined as an anastomosis between the choroidal artery, either anterior or posterior, and the medial end of the medullary artery. A positive indicator of choroidal anastomosis in the lateral view of the angiography is extreme dilation and extension of the anterior or lateral posterior choroidal artery with sudden deviation beyond the shape of the lateral ventricle at its peripheral portion in order to connect to the medullary artery (Figs. 1–3); in the anterior-posterior view, this collateral has a typical sharp inflection to the lateral. Extreme extension of the anterior choroidal or lateral posterior choroidal artery toward the body of the ventricle and the connection between the medial posterior choroidal artery and the pericallosal artery were also considered indicators of the presence of a choroidal collateral.

Involvement of the posterior cerebral artery (PCA) was identified through angiography according to our previous definition.[4,5] The angiographic Suzuki stage[17] was also graded. Other baseline variables, including patient age, sex, and diagnoses of hypertension, diabetes mellitus, and hyperlipidemia, were also recorded.

The outcome variable was de novo hemorrhage occurring during the 5-year follow-up period. A hemorrhagic event during follow-up, occurring in either hemisphere, was the secondary endpoint in the original randomized controlled trial. The imaging board extracted from these hemorrhagic events only those occurring in the previously nonhemorrhagic hemisphere after categorizing the newly

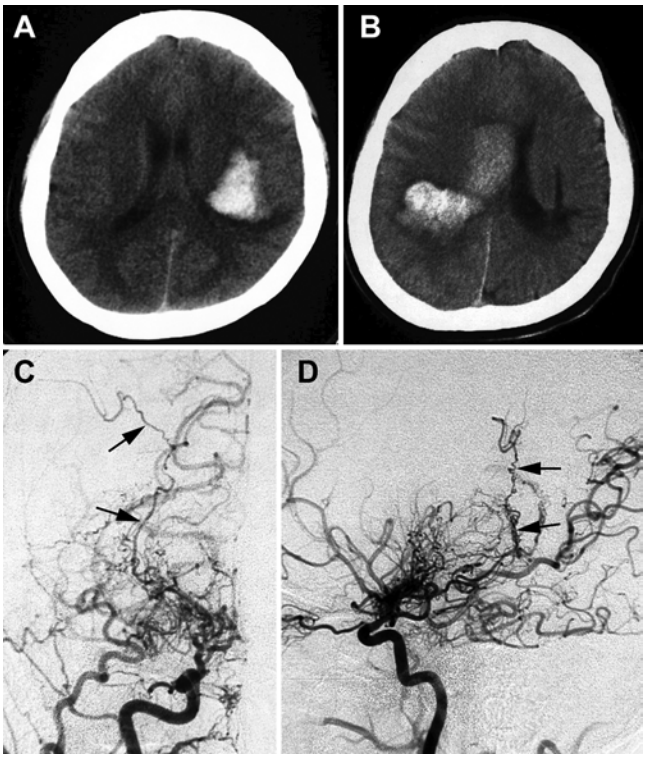

FIG. 1. A 37-year-old woman treated conservatively and suffering de novo hemorrhage in the nonhemorrhagic hemisphere. **A:** CT image at enrollment revealing hemorrhage in the left periventricular area of the posterior part of the lateral ventricle. **B:** CT image obtained 3.5 years after enrollment revealing de novo hemorrhage in the nonhemorrhagic hemisphere (right hemisphere). The de novo hemorrhage is located in the right periventricular area of the posterior part of the lateral ventricle, corresponding to the distribution of the choroidal anastomosis. **C and D:** Anterior-posterior (C) and lateral (D) views of baseline right internal carotid angiography showing the typical finding of choroidal anastomosis, extreme dilation, and extension of the anterior choroidal artery with sudden deviation from the shape of the lateral ventricle at its peripheral portion (*arrows*).

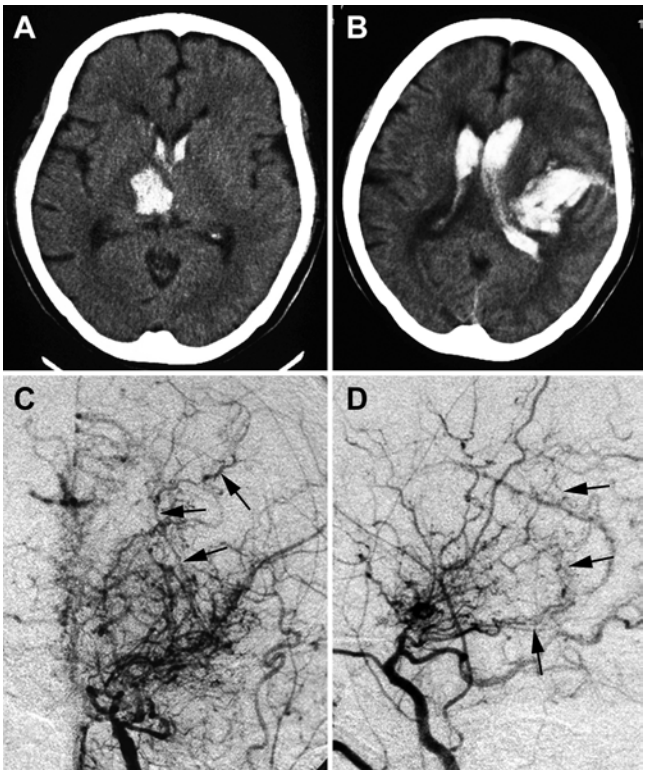

FIG. 2. A 54-year-old woman treated conservatively and suffering de novo hemorrhage in the nonhemorrhagic hemisphere. **A:** CT image at enrollment revealing hemorrhage in the right thalamus. **B:** CT image obtained 3.3 years after enrollment revealing de novo hemorrhage in the nonhemorrhagic hemisphere (left hemisphere). The de novo hemorrhage is located in the left periventricular area of the atrium of the lateral ventricle, corresponding to the distribution of the choroidal anastomosis. **C and D:** Anterior-posterior (C) and lateral (D) views of baseline left common carotid angiography showing extreme dilation and extension of the anterior choroidal artery with sudden deviation from the shape of the lateral ventricle at its peripheral portion (*arrows*), suggesting a positive finding of choroidal anastomosis.

hemorrhagic hemisphere as either right or left. De novo hemorrhage was assessed in all nonhemorrhagic hemispheres.

Statistical Analysis

The t-test, chi-square test, Mann-Whitney U-test, or Fisher's exact test was applied to compare baseline characteristics. The person-years method was used to calculate the incidence (annual risk) of de novo hemorrhage, and the Kaplan-Meier method was used to estimate 5-year cumulative incidences. The log-rank test was applied to compare Kaplan-Meier curves. If a patient suffered recurrent hemorrhage in the hemorrhagic hemisphere, survival times (times-to-event) in the nonhemorrhagic hemisphere were censored at that time.

A supplementary analysis, similar to that of our earlier study,[4] was performed to evaluate the success of extracranial-intracranial bypass in preventing de novo hemorrhage in choroidal-anastomosis-positive nonhemorrhagic hemispheres. For this analysis, we included the data for the nonhemorrhagic hemispheres included in the surgical group.

Two-sided values of $p < 0.05$ were considered significant. All analyses were performed with IBM SPSS Statistics Desktop (version 22; IBM Corp.).

Results

Among 38 patients allocated to the nonsurgical arm in the JAM Trial, 1 patient was excluded from the analysis because of the loss of the original angiographic imaging data and 1 nonhemorrhagic hemisphere was excluded because of a history of hemorrhage before enrollment (Fig. 4). As a result, the nonhemorrhagic hemispheres of 36 patients were included in the present analyses. The 36 hemispheres comprised 17 right and 19 left hemispheres. Seven patients indicated a history of transient ischemic attack (TIA) attributable to the nonhemorrhagic hemisphere.

Baseline angiography revealed choroidal anastomosis in 15 of the 36 hemispheres (41.7%, Table 1). The baseline

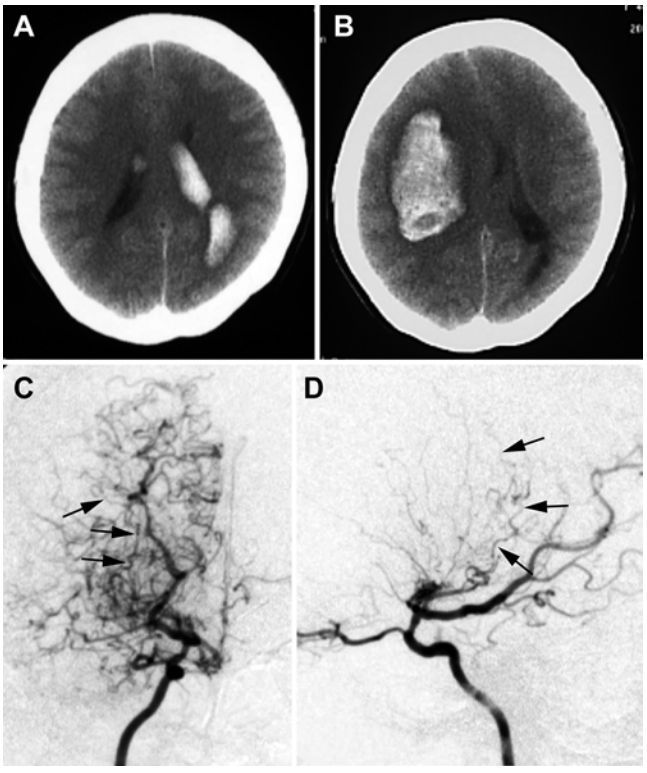

FIG. 3. A 43-year-old woman treated conservatively and suffering de novo hemorrhage in the nonhemorrhagic hemisphere. **A:** CT image at enrollment revealing hemorrhage in the left occipital area. **B:** CT image obtained 1.7 years after enrollment revealing de novo hemorrhage in the nonhemorrhagic hemisphere (right hemisphere). The de novo hemorrhage extends from the right periventricular area of the posterior part of the lateral ventricle, corresponding to the distribution of the choroidal anastomosis. **C and D:** Anterior-posterior (C) and lateral (D) views of baseline right internal carotid angiography showing extreme dilation and extension of the anterior choroidal artery with sudden deviation from the shape of the lateral ventricle at its peripheral portion (*arrows*), suggesting a positive finding of choroidal anastomosis.

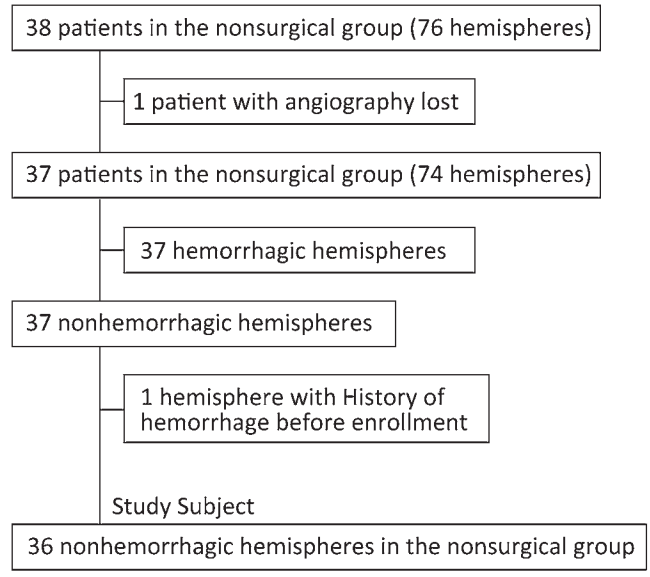

FIG. 4. Flow diagram for study inclusion.

characteristics of the study patients, including age, sex, history of TIA, and diagnoses of hypertension, diabetes mellitus, and hyperlipidemia, as well as PCA involvement, did not differ significantly between the choroidal-anastomosis-positive and -negative groups (Table 1). Regarding Suzuki stage, 4 hemispheres (11.1%) were identified as below stage 3, 11 (30.6%) at stage 3, 17 (47.2%) at stage 4, and 4 (11.1%) above stage 4. Suzuki stage did not differ significantly between the choroidal-anastomosis-positive and -negative groups (Table 1).

Among all 36 nonhemorrhagic hemispheres, de novo hemorrhage occurred in 3 hemispheres (8.3%) during the 5-year follow-up. The incidence of de novo hemorrhage in the nonhemorrhagic hemispheres was 3/148.3 person-years or 2.0% per year (Fig. 5). The 5-year cumulative incidence of de novo hemorrhage in the nonhemorrhagic hemispheres estimated by the Kaplan-Meier method was 9.8%.

All 3 hemispheres exhibiting de novo hemorrhage had been included in the choroidal-anastomosis-positive group (Figs. 1–3), whereas no hemisphere in the choroidal-anastomosis-negative group exhibited de novo hemorrhage. Kaplan-Meier analysis revealed that the choroidal-anastomosis-positive group had a significantly higher incidence of de novo hemorrhage than did the choroidal-anastomosis-negative group (5.8% per year vs 0% per year; p = 0.017; Fig. 6). The 5-year cumulative incidence of de novo hemorrhage in the choroidal-anastomosis-positive group was 26.7%. A multivariate analysis using Cox proportional hazards regression was impossible because the event incidence was zero in the choroidal-anastomosis-negative group and the calculation of the hazard ratio did not converge.

All hemorrhages occurring in the choroidal-anastomosis-positive group were located at the periventricular area of the atrium or the posterior part of the body of the lateral ventricle, a location that is anatomically compatible with the typical distribution of choroidal anastomosis (Figs. 1–3). All members of the imaging board agreed with this anatomical consistency.

Supplementary Analysis: Comparison Between Surgical and Nonsurgical Nonhemorrhagic Hemispheres Within Choroidal-Anastomosis-Positive Strata

Regarding the 42 patients allocated to the surgical group, the nonhemorrhagic hemisphere was undetermined in 4 patients because of midline hemorrhage or diffusely distributed intraventricular hemorrhage. In the 38 patients with the remaining 38 nonhemorrhagic hemispheres, 3 patients had a history of hemorrhage before enrollment. Accordingly, the 35 patients with nonhemorrhagic hemispheres receiving surgery were extracted. Among them, choroidal anastomosis was identified in 10 hemispheres (28.6%), and none of these choroidal-anastomosis-positive patients subsequently suffered de novo hemorrhage after surgery during the 5-year follow-up. The incidence is thus low compared to that in the patients with choroidal-anastomosis-positive nonhemorrhagic hemispheres receiving

TABLE 1. Baseline variables of 36 nonhemorrhagic hemispheres treated conservatively

	Choroidal Anastomosis		
	Positive	Negative	p Value
No. of hemispheres	15	21	
Mean age in yrs ± SD	41.2 ± 13.2	42.3 ± 11.8	0.801
Female	12 (80.0)	14 (66.7)	0.379
Hypertension	4 (26.7)	3 (14.3)	0.355
Diabetes mellitus	1 (6.7)	1 (4.8)	1.000
Hyperlipidemia	1 (6.7)	1 (4.8)	1.000
PCA involvement	5 (33.3)	4 (19.1)	0.329
History of TIA	4 (26.7)	3 (14.3)	0.355
Median Suzuki stage	4	4	0.340

Values are number (%) of hemispheres unless otherwise indicated.

medical treatment alone (5.8% per year), although the difference was not statistically significant in the Kaplan-Meier analysis (p = 0.119; Fig. 7).

Discussion

According to our results, the annual risk of de novo hemorrhage in the nonhemorrhagic hemisphere of a patient with hemorrhagic moyamoya disease is estimated at 2.0%. The results of Kaplan-Meier analyses suggest that a nonhemorrhagic hemisphere with choroidal anastomosis is at higher risk of de novo hemorrhage than one without. The correspondence of the distribution of choroidal anastomosis and hemorrhage suggests that choroidal anastomoses are responsible for de novo hemorrhages.

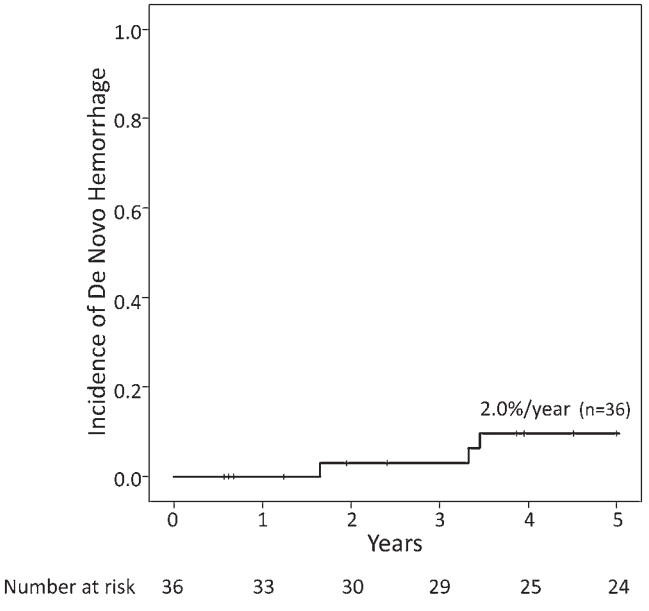

FIG. 5. Kaplan-Meier curve for de novo hemorrhage in all nonhemorrhagic hemispheres treated conservatively. Censored subjects are indicated by *tick marks*.

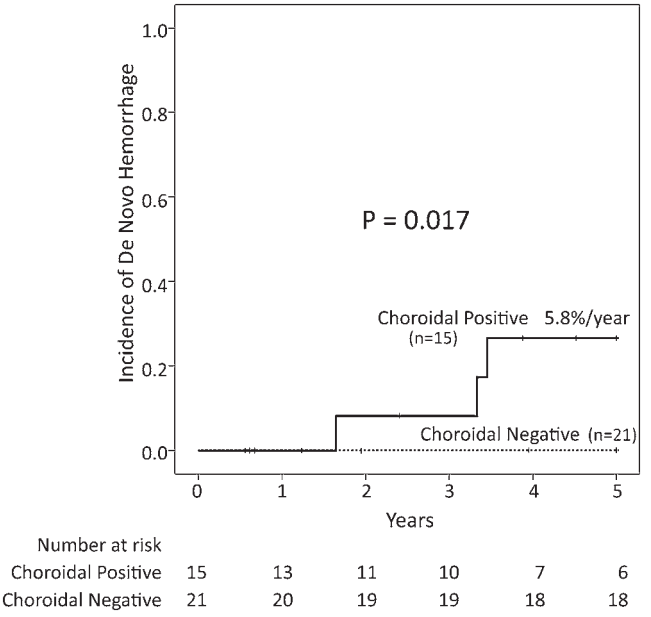

FIG. 6. Kaplan-Meier curves for de novo hemorrhage in the choroidal-anastomosis-positive and -negative nonhemorrhagic hemispheres treated conservatively. Censored subjects are indicated by *tick marks*.

The issue of de novo hemorrhage in the nonhemorrhagic hemisphere has received little attention. Liu et al. addressed this issue by comparing the incidence of subsequent hemorrhage in the hemorrhagic and nonhemorrhagic hemispheres.[11] Their Kaplan-Meier estimate of the

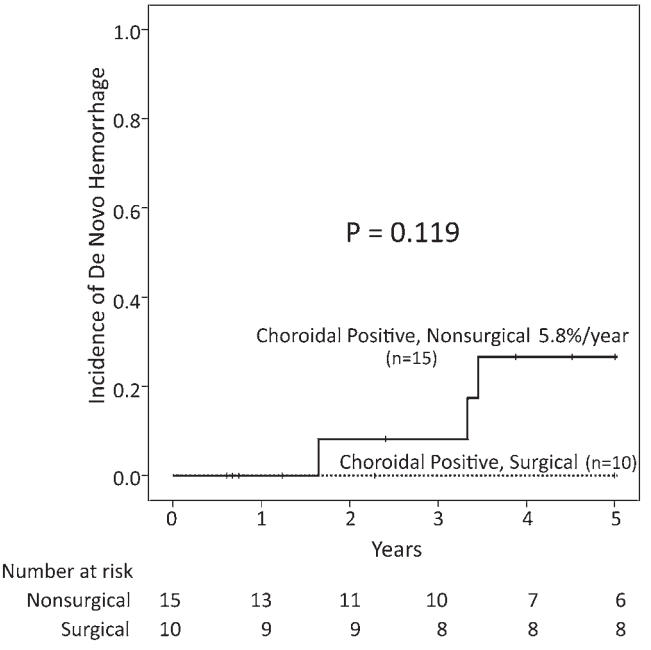

FIG. 7. Supplementary analysis: Kaplan-Meier curves for de novo hemorrhage with the choroidal-anastomosis-positive nonhemorrhagic hemispheres treated surgically and conservatively (n = 25). Censored subjects are indicated by *tick marks*.

occurrence of subsequent hemorrhage in the nonhemorrhagic hemisphere was 4.1% during a mean follow-up period of 6.33 years. Our estimate (9.8% in 5 years) is higher than theirs. This divergence is attributable to the demographic difference between the two studies: the study by Liu et al. predominantly included hemispheres undergoing bypass surgery, while ours included hemispheres treated conservatively. More recently, Kim et al. estimated the 5-year risk of de novo hemorrhage in the nonaffected hemisphere as 8.3%.[8] Their study included only patients treated conservatively, and our estimate (9.8% in 5 years) is very similar to theirs.

Interestingly, the annual risk of de novo hemorrhage estimated in the present analysis (2% per year), reflecting the natural outcome of the nonhemorrhagic hemisphere in hemorrhagic moyamoya disease, is quite similar to that for asymptomatic moyamoya disease. Kuroda et al. reported in their multicenter survey of asymptomatic moyamoya disease that the annual incidence of any stroke (hemorrhagic or ischemic) was 3.2%.[10] Although these authors did not separately calculate the incidence of hemorrhagic stroke, the annual risk of hemorrhagic stroke is approximately 2% per year because hemorrhagic stroke accounted for 3 of the 4 strokes overall. Cho et al. reported in their retrospective cohort study that the annual risk of de novo hemorrhage occurring in 35 asymptomatic patients treated conservatively was 2.5%.[1]

Our results are in line with those of previous studies demonstrating that choroidal collaterals are at high risk of rupture. Irikura et al. and Morioka et al. demonstrated in cross-sectional studies that choroidal collaterals are seen more frequently in hemorrhagic rather than ischemic moyamoya disease.[7,14] Our earlier longitudinal analysis, including the nonsurgical cohort of the JAM Trial, revealed that choroidal anastomosis was a predictor of rebleeding in hemorrhagic moyamoya disease.[5] Our most recent case-control analysis comparing hemorrhagic and ischemic populations revealed through multivariate analyses that choroidal collaterals are the one characteristic significantly associated with hemorrhagic moyamoya disease.[2]

From a clinical perspective, our results are significant in the following two respects. First, our results might underline the possibility of choroidal anastomosis serving as an indicator of bypass surgery for the nonhemorrhagic hemisphere in hemorrhagic patients. The overall result of the JAM Trial, the protocol for which required bilateral surgery, revealed the benefit of surgery in preventing recurrent hemorrhage.[12] In terms of following the protocol, bilateral surgery on both the hemorrhagic and nonhemorrhagic hemispheres is recommended. Due to the nature of subset analysis, our analysis within the choroidal-anastomosis-positive strata (Fig. 7) might lack sufficient statistical power to answer whether bypass surgery is indicated for the choroidal-anastomosis-positive nonhemorrhagic hemisphere. Yet our results provide the valuable insight that the risk of de novo hemorrhage in the nonhemorrhagic hemisphere should not be underestimated, especially when choroidal anastomosis is present. Bypass surgery for the nonhemorrhagic hemisphere in hemorrhagic patients might be considered at least when choroidal anastomosis is present, although this recommendation should be validated in a larger study. In the clinical setting, other factors, such as existence of TIA or compromised cerebral blood flow, might also influence the indication for bypass surgery in the nonhemorrhagic hemisphere.

Second, our results might lead to an important hypothesis regarding asymptomatic and less-symptomatic patients. Given that a nonhemorrhagic hemisphere resembles an asymptomatic one, choroidal anastomosis might also be a predictor of de novo hemorrhage in asymptomatic patients. The annual risk of de novo hemorrhage in asymptomatic moyamoya disease is comparable to that of other hemorrhagic cerebrovascular disorders such as intracranial aneurysm (approximately 1% per year)[15] and arteriovenous malformation (2.6% per year).[13] Choroidal anastomosis might be of use in risk stratification of asymptomatic moyamoya disease. Intracranial hemorrhage is the most significant factor related to poor outcome in moyamoya disease.[6] If asymptomatic patients with choroidal anastomosis are at substantial risk of subsequent de novo hemorrhage, preventive treatment might be considered for the subgroup. This hypothesis should be tested in future studies.

The present study has several limitations. As discussed above, some of the present subset analyses might lack sufficient statistical power to test the hypothesis because only data of nonhemorrhagic hemispheres treated conservatively were extracted from the original trial. A multivariate analysis using Cox proportional hazards regression was impossible because the event incidence was zero in the choroidal-anastomosis-negative group and the calculation of the hazard ratio did not converge. Larger studies are required to confirm that choroidal collateral vessels are a predictor of de novo hemorrhage.

Conclusions

The results of the present preliminary analysis regarding hemorrhagic moyamoya disease suggest that the annual risk of de novo hemorrhage in the nonhemorrhagic hemisphere is similar to that in asymptomatic moyamoya disease. The results also suggest that the presence of choroidal collateral vessels affects the risk of de novo hemorrhage in the nonhemorrhagic hemisphere, although this should be verified in larger studies. Further studies are needed to identify risk factors of de novo hemorrhage and determine the optimal treatment strategy for nonhemorrhagic hemispheres and asymptomatic patients.

Acknowledgments

The JAM Trial has been funded since 1999 by a grant from the Japanese Ministry of Health, Labour, and Welfare as a major project of the Research Committee on Spontaneous Occlusion of the Circle of Willis (moyamoya disease).

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Miyamoto, Funaki. Acquisition of data: Miyamoto, Funaki, Takahashi, Kuroda, Fujimura. Analysis and interpretation of data: all authors. Drafting the article: Funaki. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Miyamoto. Statistical analysis: Tomata.

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