Background and Purpose—Evidence on the natural history of hemorrhagic moyamoya disease is still insufficient. We investigated the incidence of recurrent intracranial bleeding, mortality, and risk factors for rebleeding in patients with moyamoya disease.

Methods—A total of 128 conservatively managed patients with hemorrhagic presentation and complete follow-up data were included. Recurrent hemorrhages during long-term follow-up were documented. Annual and cumulative incidence rate of bleeding was generated via Kaplan-Meier survival analysis, and risk factors were analyzed using logistic regression analysis.

Results—The median follow-up time was 10.1 (1–27) years. During a total of 1300.7 patient-years, 47 (36.7%) patients experienced 59 occurrences of recurrent hemorrhages, rendering an average annual incidence of 4.5%. Among them, 9 patients (19.1%) died from rebleeding and 12 patients sustained severe disability (modified Ranking scale score of ≥3). The cumulative risk of rebleeding was 7.8% at 5 years, 22.6% at 10 years, and 35.9% at 15 years. Only 4 (3.1%) patients experienced ischemic stroke, yielding an average annual incidence of 0.3%. Multivariate analysis showed that smoking (odds ratio, 4.85; P=0.04) was an independent risk factor of rebleeding. Rebleeding (hazard ratio, 11.04; P=0.02) and hypertension (hazard ratio, 4.16; P=0.04) were associated with increased mortality. Age, type of initial bleeding, digital subtraction angiography staging, family history, and coexisting cerebral aneurysms were not associated with increased risk of rebleeding.

Conclusions—Rebleeding events were common and the main cause of death in patients with hemorrhagic moyamoya disease. The risk of rebleeding steadily increased during long-term follow-up. Smoking was a risk factor for rebleeding, and hypertension was associated with increased mortality.

in incidence hemorrhagic risk based on long-term natural history, such as the rebleeding rate, cumulative incidence, and risk factors. To better chart the natural course of the disease, we observed the clinical course of 128 patients over a long-term follow-up.

Methods

Patients and Materials

The data that support the findings of this study are available from the corresponding author on reasonable request.

We conducted a retrospective study with long-term follow-up assessing the natural history of hemorrhagic MMD. This study was approved by the Beijing Tiantan Hospital Institutional Review Board. The goal is to determine the risk of recurrent hemorrhages. From 1985 to 2012, a total of 274 patients with hemorrhagic MMD were identified in Beijing Tiantan Hospital. Among them, 128 patients who were treated conservatively were included in this study. The diagnosis of MMD was based on digital subtraction angiography (DSA). All patients initially presented with intracranial hemorrhage, which was confirmed by brain computed tomographic (CT) scan. It should be noted that Beijing Tiantan Hospital is one of the major referral centers for MMD in China; therefore, most patients in our study cohort were not in the acute stage of hemorrhage. Conservative treatment is determined on a basis of shared decision-making between physicians and patients and their family members. Provided with the rarity of disease, there was no specific treatment protocol established for these patients. Patients with ischemic symptoms as the initial presentation, pseudo-MMD, and moyamoya syndrome caused by other systemic diseases were excluded.

Follow-Up Methods

Baseline clinical characteristics and imaging data were reviewed, including age, sex, risk factors (hypertension, family history of MMD, smoking, drinking, and coexisting intracranial aneurysms), disease stage based on DSA review, and types of hemorrhage (intracerebral hemorrhage, intraventricular hemorrhage, and subarachnoid hemorrhage). All patients were solicited for annual follow-up visits in outpatient clinic. At each visit, brain CT angiography or magnetic resonance angiography was performed to evaluate cerebral vessels. In addition, brain CT scans were performed when patients experienced a recurrent hemorrhage. Overall, all patients had completed annual follow-up visits in outpatient clinic at the first 3 years. For patients who were unavailable for in-person interviews, we attempted to obtain basic clinical information over the phone for the assessment of onset of rebleeding, ischemic events, and survival status. The time interval from the initial episode to rebleed, site and treatment of recurrent hemorrhage were investigated. The following items constitute primary end points: (1) patient's death from recurrent bleeding or other medical cause and (2) patients who received bypass surgery. Clinical functional outcome after hemorrhage was recorded using the modified Rankin scale.

Data Analysis

All analyses were conducted using IBM SPSS statistical software (version 19.0). The average annual rebleeding rate was calculated by dividing the number of recurrent hemorrhage events from the initial episode by patient-years. Logistic regression was used to generate odds ratios (ORs) and 95% CIs. Cumulative risk of rebleeding and survival curves were estimated by the Kaplan-Meier product-limit method. Log-rank test statistics were used to determine whether Kaplan-Meier transition curves differed among subgroups. A logistic regression model was built to identify predictors of rebleeding. Cox proportional hazards models were used to calculate multivariate hazard ratios for survival. The primary end points were any deaths from MMD, including lethal hemorrhagic stroke, cerebral infarction, and other fatal events. Patients who were alive at the end of the follow-up period, lost to follow-up, and deaths from other disease were considered censoring events. Information on variables was collected before follow-up and included age (continuous variable), sex, types of hemorrhage, coexisting with intracranial aneurysms, cigarette-smoking status or alcohol consumption, a family history of MMD, hypertension (systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg, or use of antihypertensive medication), DSA stage, and characteristics of brain CT perfusion. A 2-tailed *P* value <0.05 was considered statistically significant.

Results

Patient Characteristics

The final cohort consisted of 128 patients. Baseline presentation and characteristics of the patient cohort are presented in Table 1. The mean age of the patients at the time of the first bleeding episode was 34.5±9.7 years (range, 8–61 years), and 95% were adult patients. The female-to-male ratio was 2:1. Intraventricular hemorrhage and intracerebral hemorrhage were the most frequent presentations observed on CT scans, accounting for 43.0% and 28.9%, respectively. The DSA stage of patients mostly were

Table 1. Patient Demographics and Baseline Characteristics Grouped by Rebleeding

Demographics	All Patients (N=128)	No Rebleeding (n=81)	Rebleeding (n=47)	*P* Value
Women, %	86 (67)	50 (61)	36 (76)	0.08
Age, y; mean±SD	34.5±9.7	35.0±9.7	33.7±9.9	0.47
History of risk factors, %				
Family MMD	9 (7.0)	5 (6.1)	4 (8.5)	0.88
Hypertension	15 (11.7)	7 (8.6)	8 (17.0)	0.15
Aneurysm	14 (10.9)	10 (12.3)	4 (8.5)	0.70
Smoking	16 (12.5)	6 (7.4)	10 (21.2)	0.02
Drinking	10 (7.8)	3 (3.7)	7 (14.8)	0.03
Types of hemorrhage, %				
ICH	37 (28.9)	20 (24.7)	17 (36.1)	0.16
IVH with ICH	22 (17.1)	15 (18.5)	7 (14.8)	0.60
IVH	55 (43.0)	38 (46.9)	17 (36.1)	0.23
SAH	14 (10.9)	8 (9.9)	6 (12.7)	0.61
DSA stage, %				
I	6 (4.6)	4 (4.9)	2 (4.2)	0.81
II	15 (11.7)	10 (12.3)	5 (10.6)	0.77
III	42 (32.8)	26 (32.0)	16 (34.0)	0.82
IV	40 (31.2)	23 (28.3)	17 (36.1)	0.36
V	23 (17.9)	16 (19.7)	7 (14.8)	0.49
VI	2 (1.5)	2 (2.4)	0	…
CT perfusion, %	117	77	40	…
Normal	14 (11.9)	8 (10.3)	6 (15.0)	0.46
CBF↓	38 (32.4)	20 (25.9)	18 (45.0)	0.03
MTT↑	103 (88.0)	69 (89.6)	34 (85.0)	0.46

CBF indicates cerebral flood flow; CT, computed tomography; DSA, digital subtraction angiography; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; MMD, moyamoya disease; MTT, mean transit time; and SAH, subarachnoid hemorrhage.

stage III and stage IV according to Suzuki classification. One-hundred seventeen patients underwent CT perfusion. Please note, the measure of CT perfusion was completed within 3 days after admission, and all patients were not in the acute stage of cerebral hemorrhage. Of them, 38 (32.4%) patients had reduction of regional cerebral blood flow (rCBF), and 103 (88%) patients had prolonged mean transit time.

Incidence of Recurrent Stroke

The median follow-up time was 10.1 (1–27) years. For a follow-up total of 1300.7 patient-years, 51 (39.8%) patients experienced recurrent stroke. Of them, 59 rebleeding events occurred in 47 patients (36.7%), yielding an annual incidence of rebleeding of 4.5%. Nineteen percent (9 of 47) of patients died because of rebleeding, whereas 35% (12 of 47) patients had severe disability (modified Rankin scale score of ≥3). None of the patients died from other diseases during follow-up period. The mean age of the 47 patients at the first rebleeding was 40±10 years (range, 13–61 years). Nine patients experienced multiple rebleeding events, which includes 7 patients having 2 events, 1 patient having 3 events, and 1 having 4 events. The interval from the first hemorrhage to the episode of rebleeding ranged from 0.1 to 20 years (mean, 6.6 years). Of them, 8 patients (17.0%) experienced rebleeding at the first year after the initial bleeding, 14 patients (29.7%) experienced rebleeding at 2 to 5 years, 14 patients (29.7%) experienced rebleeding at 6 to 10 years, and 11 patients (23.4%) experienced rebleeding >10 years after the first hemorrhage. The time interval distributions of 59 episodes of rebleeding are shown in Figure 1. The cumulative risk of rebleeding was 7.8% at 5 years, 22.6% at 10 years, and 35.9% at 15 years. Kaplan-Meier curves for rebleeding-free survival and given baseline characteristics are shown in Figures 2 and 3. Only 4 (3.1%) patients experienced ischemic stroke, yielding an average annual incidence of 0.3%.

Risk Factors Associated With Rebleeding and Mortality

Univariable and mutivariable ORs for the risk factors of rebleeding are shown in Table 2. Univariate analysis showed

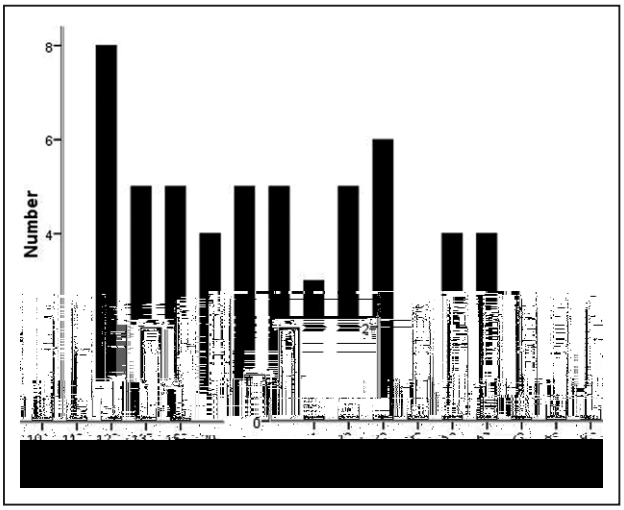

Figure 1. The distribution of the time interval from initial hemorrhage to rebleeding (years).

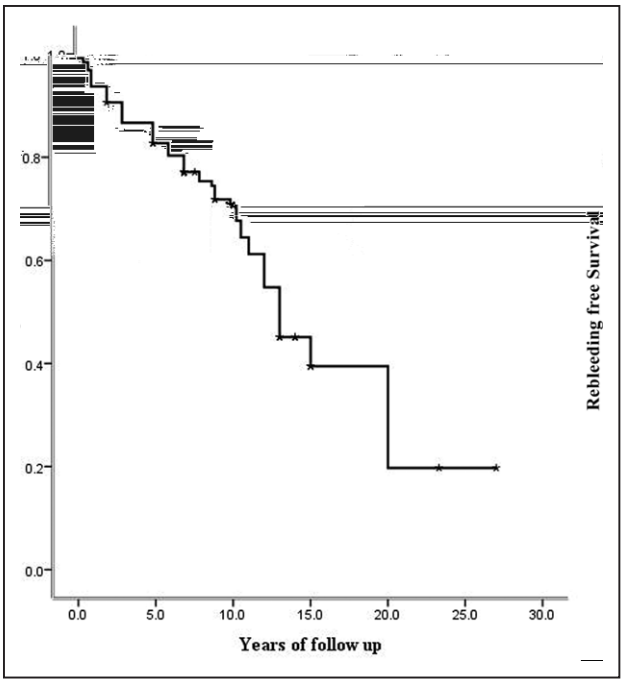

Figure 2. Kaplan-Meier curve for cumulative rates of rebleeding for all patients.

that decreased rCBF (OR, 2.33; 95% CI, 1.04–5.21; *P*=0.03), smoking (OR, 3.37; 95% CI, 1.14–10.00; *P*=0.02), and drinking (OR, 4.55; 95% CI, 1.11–18.54; *P*=0.03) were associated with rebleeding. However, multivariate analysis showed only smoking (OR, 4.85; 95% CI, 1.02–23.00; *P*=0.04) was associated with a significantly increased risk of rebleeding, and drinking (OR, 6.02; 95% CI, 0.95–37.80; *P*=0.05) showed a trend toward significance. Age, types of the initial bleeding, DSA stage, hypertension, family history of MMD, and coexisting intracranial aneurysms were not associated with any increased risk of rebleeding in analysis (*P*>0.05). Table 3 provided the associations of risk factors with mortality. Subjects with rebleeding had an 11.04-fold risk of death in comparison with those without rebleeding (hazard ratio, 11.04; 95% CI, 1.30–93.67; *P*=0.02). Multivariate analysis showed sex was associated with mortality (*P*<0.01), although there was no significant difference in univariate analysis (*P*=0.32). It should be noted that there was no significant difference between men and women if removed the impact of rebleeding in the Cox regression analysis (*P*=0.08). The Kaplan-Meier curve for survival for the entire cohort is shown in Figure I in the online-only Data Supplement. The mortality in patients with hypertension was 26.6% (4/15), which was much higher than the mortality (4.4%, 4/113) in patients without hypertension. Cox model and Kaplan-Meier analysis showed that hypertension was an independent risk factor for death (hazard ratio, 4.1; 95% CI, 1.07–16.87; *P*=0.04; Table 3; Figure I in the online-only Data Supplement).

Discussion

The current goal of treatment for hemorrhagic MMD is to decrease mortality and preserve neurological function by preventing recurrent intracranial hemorrhages. Therefore,

understanding the natural history of hemorrhagic MMD in respect to the risk of rebleeding is crucial. However, given the rarity of this disease, existing knowledge on the natural history of hemorrhagic MMD is limited. In current study, we followed 128 patients with hemorrhagic MMD who were treated conservatively through a relatively long follow-up period. As shown in results, rebleeding occurs in ≈40% of our study cohort. Our findings suggest that the natural history of hemorrhagic MMD remains dynamic, and long-term follow-up is needed to fully appreciate the risk of rebleeding.

Rebleeding is the main cause of mortality in hemorrhagic MMD. There is considerable concern for high risk of recurrent hemorrhages in these patients given the exposure of prior hemorrhages. In this study, 47 patients (36.7%) underwent rebleeding events during follow-up, and 9 died as a result. The frequency of rebleeding is within the range (16%–66%) of previous studies.[3–6] Our data also suggest that rebleeding is the most important factor associated with poor prognosis in patients with hemorrhagic MMD.

Previous studies have demonstrated a widely variable range of rebleeding risk. One reason for this variation might be related to the random effects associated with rare events in studies that only have a short-term follow-up, as it often requires long-term follow-up to facilitate observation of such events. Interesting5.1i.ly v

first year, and 6 rebleeding events occurred at the tenth year after the first hemorrhage (Figure 1). The number of patients with recurrent hemorrhages did not decrease along with extended follow-up time. Therefore, based on this observation, we recommend at least 10 years of follow-up to fully appreciate the risk of recurrent hemorrhage in MMD patients with hemorrhagic presentations. Accordingly, it may be extrapolated that hemorrhagic MMD patients who were treated surgically will also need similar length of follow-up to ascertain treatment effect on hemorrhagic risk.

The exact mechanism for hemorrhage in MMD has not been fully elucidated. Previous studies have revealed that the rupture of microaneurysm and moyamoya vessels were related to the hemorrhagic presentation in patients with MMD[11–13]; 0.247 Tw 0 -1.211 TD [(related to the hemorrre)2 occurreation in patients [(firstf5 K2ccu Tw 1.5 -1.21osent1.211 TD (lat

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