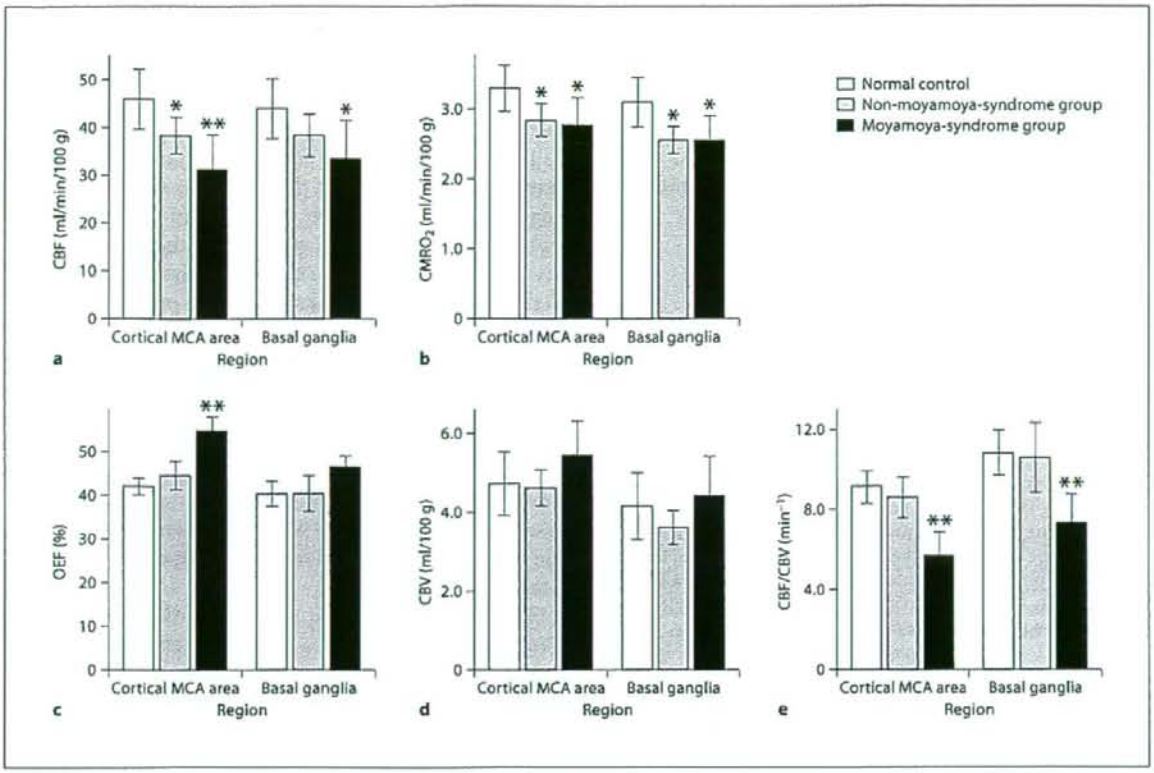

Fig. 2. Comparison of the regional CBF (**a**), regional $CMRO_2$ (**b**), regional OEF (**c**), regional CBV (**d**) and CBF divided by CBV (CBF/CBV; **e**) by the angiographic type. Data are shown as means plus 95% confidence intervals. Cortical MCA area = the ipsilateral cortical middle cerebral artery (MCA) branch territory in the frontal, parietal, and temporal lobes; basal ganglia = the ipsilateral basal nuclei except for the caudate nucleus. * $p < 0.05$ (one-way ANOVA followed by least significant difference test) versus normal control; ** $p < 0.05$ (ANOVA, least significant difference test) versus non-moyamoya-syndrome group and normal control.

moya-syndrome group in the cortical MCA area ($p = 0.03$) and the basal ganglia ($p = 0.04$), as determined by Mann-Whitney's U test. A significantly reduced CBF/CBV was found in the moyamoya syndrome group as compared with the non-moyamoya-syndrome group and normal controls in the whole MCA area. The atherosclerotic lesions in the ipsilateral hemisphere were more advanced in severity in the moyamoya syndrome group (table 1), and the total vascularity index was significantly lower in the moyamoya syndrome group than in the non-moyamoya-syndrome group ($p = 0.01$; table 1). Collateral flow from the external carotid artery to the ICA via retrograde flow through the ophthalmic artery was found only in patient No. 6. There was a weak negative correlation between the OEF in the cortical MCA area and the total vascularity index ($p = 0.06$). Multivariate linear regression analysis revealed that the OEF in the cortical MCA area remained significantly higher in the moyamoya syndrome group, even after controlling for the ACA, MCA and PCA vascularity indices ($p = 0.002$). In the moyamoya syndrome group, there was a significant correlation between the basal moyamoya-like vessel extension index and the OEF in the cortical MCA area ($r > 0.999$, $p < 0.001$; fig. 3); this correlation remained significant even after adjustment for the total vascularity index ($p = 0.02$).

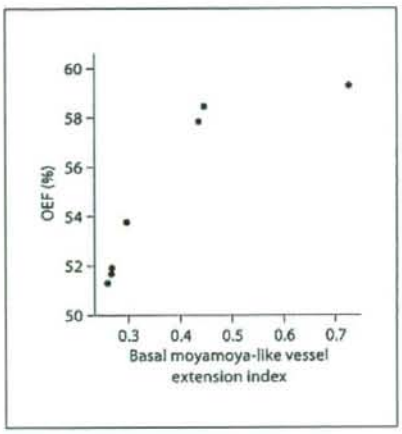

Fig. 3. The extent of the development of angiographic basal moyamoya-like vessels in the moyamoya syndrome group was evaluated by DSA. The ratio of the distance from the root to the top-end of the basal moyamoya-like vessels to the distance from the base of the skull (top of the sella turcica) to the top of the skull in the same plane was indicated as the basal moyamoya-like vessel extension index. Regional OEF was measured by positron emission tomography in the cortical MCA area.

Discussion

The hemodynamic and metabolic backgrounds of moyamoya syndrome associated with atherosclerosis have not yet been investigated. In the present study, we aimed to elucidate the hemodynamic and metabolic changes associated with moyamoya syndrome with atherosclerosis, and evaluated the hemodynamic and metabolic changes associated with the development of the moyamoya-like vascular abnormality associated with unilateral atherosclerotic steno-occlusive lesions of the ICA or MCA in the chronic phase. We demonstrated that the cerebral hemodynamic impairment was significantly more severe in patients with moyamoya syndrome than in those without moyamoya syndrome.

We demonstrated previously that among cases of moyamoya disease, the OEF was significantly higher in adult patients with extensively developed basal moyamoya vessels than in those with less extensive development of moyamoya vessels and normal controls [2]. According to a perfusion-weighted MRI study [3], the extent of development of moyamoya vessels in both childhood and adult moyamoya disease was correlated with the mean transit time, which has been shown to be an alternative index to the OEF [11]. In the present study, it was demonstrated that the presence and extent of development of the moyamoya-like vessels were also correlated with the severity of the cerebral hemodynamic impairment in the ipsilateral cortical MCA territory.

It has been shown that in moyamoya disease, the extent of development of the basal moyamoya vessels is negatively correlated with the extent of development of leptomeningeal collateral vessels from the PCA, and positively correlated with the severity of the stenotic lesions in the major arterial trunks [12]. In the present study, the degree of the total vascularity, excluding that of the moyamoya-like vessels, in the ipsilateral hemisphere was significantly worse in the moyamoya syndrome group than in the non-moyamoya-syndrome group. Both in moyamoya disease and in moyamoya syndrome, the basal moyamoya or moyamoya-like vessels, which are considered to be types of collateral vessels in moyamoya disease [5, 13], were found to have developed to complement the insufficient collateral networks in the ipsilateral cortical area.

The present study had some limitations. Firstly, the number of patients was so small that statistical reliability could not be ensured. Secondly, the normal controls enrolled in this study were younger than the patient group. In this study, however, we focused on comparisons between the patient groups, because there have been numerous comparative studies about cerebral hemodynamic and oxygen metabolism by PET between normal controls and patients with atherosclerotic steno-occlusive lesions. Thirdly, the ROI settings by the automated ROI analysis program FineSRT are sometimes inappropriate because of errors in normalization procedures, brain atrophy by aging, artifacts by gas masks or displacement of sinuses. In the present study, we visually checked all the ROI settings via the viewer window and eliminated apparently inappropriate ROI from the analysis. Fourthly, although we have suggested that cerebral hemodynamic compromise may be responsible for the development of moyamoya-like vessels, hereditary factors may also be involved in this angiogenesis because the incidence of moyamoya disease is comparatively higher in the Japanese [13] and Koreans [14], and markedly lower in Caucasians. Further studies are needed to elucidate the effects of racial differences and genetic factors on the development of moyamoya-like vessels.

Conclusion

The hemodynamic and metabolic backgrounds of moyamoya syndrome associated with atherosclerosis have not yet been investigated. The present study clarified that the development of the basal moyamoya-like vascular abnormality is an important sign of misery perfusion in the ipsilateral cortical MCA territory in patients with moyamoya syndrome associated with unilateral chronic atherosclerotic steno-occlusive lesions.

Acknowledgments

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THE PRESENCE OF MULTIPLE MICROBLEEDS AS A PREDICTOR OF SUBSEQUENT CEREBRAL HEMORRHAGE IN PATIENTS WITH MOYAMOYA DISEASE

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OBJECTIVE: To examine the relationship between asymptomatic microbleeds (MBs) and the occurrence of subsequent stroke in patients with moyamoya disease.

METHODS: Beginning in October 2003, 50 consecutive patients with moyamoya disease were enrolled in a prospective study using 3-T magnetic resonance imaging. These patients were followed from the date of the initial magnetic resonance study until the date of the first subsequent stroke or final magnetic resonance study. The median follow-up period was 15 months. The patients were comprised of 13 men and 37 women ranging in age from 9 to 68 years (mean age, 40.5 ± 16.2 yr).

RESULTS: Although no MBs were found in 27 patients in the initial magnetic resonance study, a total of 66 MBs were found in the remaining 23 patients. Eleven patients had a single MB and 12 had multiple MBs. The patients were divided into three groups according to the number of MBs: a non-MB group, a single-MB group, and a multi-MB group. Kaplan-Meier curves of the three groups showed a significantly higher likelihood of subsequent hemorrhage in the multi-MB group than in either the non-MB or single-MB groups ($P = 0.0380$). No significant differences among the three groups were seen in terms of their subsequent infarction-free ratios. Age-adjusted analysis performed with the Cox proportional hazard model also showed the presence of multiple MBs as an independent risk factor (hazard ratio, 2.89; 95% confidence interval, 1.001–13.24).

CONCLUSION: The presence of multiple MBs might be a predictor of subsequent hemorrhage in patients with moyamoya disease. Confirmation of these results will require a study with a larger number of patients and a longer follow-up period.

KEY WORDS: Cerebral hemorrhage, Magnetic resonance imaging, Microbleeds, Moyamoya disease

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Moyamoya disease (MMD) has been considered a progressive steno-occlusive disease in the terminal portion of the bilateral internal carotid arteries occurring with the development of moyamoya vessels (9). Although cerebral hemorrhage is considered the most significant event contributing to a poor prognosis or death in this entity, the origin of the hemorrhage mechanism has not been fully elucidated (26, 33). Gradient-echo T2*-weighted magnetic resonance imaging (MRI) is extremely sensitive at detecting small remnants of previous cerebral microbleeds (MBs) (8, 11). MBs are usually defined as small, rounded, foci appearing hypointense on T2*-weighted images that are distinct from vascular flow voids, leptomeningeal hemosiderosis, and nonhemorrhagic subcortical mineralization (55). MBs have been regarded as a general marker of microvascular vulnerability (2, 7, 16, 49, 50). We previously reported that, in a 3-T MRI study, the incidence of asymptomatic MBs was significantly higher in patients with MMD than in healthy individuals (29). In the present study using 3-T MRI scans, we show the early results of our prospective study of MBs in patients with MMD to investigate the association between MBs and the risk of future hemorrhagic events.

PATIENTS AND METHODS

Patients

Beginning in October 2003, 50 consecutive patients with MMD admitted to the Department of Neurosurgery, Kyoto University Graduate School of

Medicine, were enrolled in a prospective follow-up study using a 3-T MRI unit (Magnetom Trio; Siemens, Erlangen, Germany). All patients were diagnosed by cerebral angiography as having MMD according to the diagnostic guideline updated in 1997 (7). The patients were 13 men and 37 women ranging in age from 9 to 68 years (mean age, 40.5 ± 16.2 yr). Before the initial MRI study, 31 patients had presented with transient ischemic attack, 17 with cerebral infarction, and 19 with cerebral hemorrhage. During the follow-up period, 37 patients were prescribed antiplatelet medication and 12 patients antihypertensive medication. A total of 23 patients had undergone revascularization surgery on both hemispheres before the initial MRI study. All revascularization surgeries were performed as superficial temporal artery-to-middle cerebral artery (STA-MCA) anastomosis with or without encephalomyosynangiosis (EMS). Three patients with cerebral aneurysms had been treated by coil embolization before the initial MRI study.

Imaging

The study and follow-up of all patients were undertaken with the same 3-T MRI unit. Our previous report described the imaging methods used for axial T2-weighted turbo spin echo sequences and axial T1-weighted three-dimensional magnetization-prepared rapid acquisition gradient-echo sequences (29). In the same studies, images were also obtained with three-dimensional time-of-flight magnetic resonance angiography (repetition time, 22 ms; flip angle, 20 degrees; single-slice acquisition; slice thickness, 0.8 mm; matrix, 512 × 208; acquisition time, 4 min 8 s) (10). An asymptomatic MB was defined as a small hypointense area (<10 mm in diameter) in the brain parenchyma with well-defined margins on the T2*-weighted images and, in cases of hemorrhagic MMD, located apart from the previous cerebral hemorrhage. Hemorrhagic masses such as cavernous angiomas and signal voids of cerebral arteries were distinguished and excluded by means of the other sequences. In patients with hemorrhagic MMD, the locations of all previous hematomas could be determined with computed tomographic (CT) studies at hemorrhage. Residues of previous hematomas were detected as hyperintense lesions surrounded by a hemosiderin rim or only hypointense lesions showing linear or irregularly shaped configurations in T2-weighted imaging studies. When T2*-weighted images revealed hypointense lesions suspected as being MBs in patients with previous hemorrhage, all lesions contiguous with the previous hematoma in T2-weighted images were excluded from the MBs. Leptomeningeal hemosiderosis on the brain surfaces of patients with previous hemorrhage and patients receiving surgery was also excluded.

Protocol of the Follow-up Study

The protocol of the MRI study was as follows: MRI scans were performed at 6 months and annually after the initial study. MRI scans were performed on 31 patients according to the protocol. Of these, 17 patients missed the study at 6 months. Thirteen patients who received bypass surgery during the follow-up period underwent optional postoperative MRI scans within 3 months of surgery to determine the effects of the surgery on the development of new MBs. Two patients in our series underwent only the initial and postoperative MRI scans.

Patient Outcomes

The entry date was defined as the date of the initial 3-T MRI study. The primary end point was defined as the first recurrent stroke attack during the follow-up period confirmed with an imaging study using CT scanning or 3-T MRI scans. Hemorrhage was confirmed with CT and cerebral infarction was confirmed with a follow-up MRI scan. The last follow-up date in patients presenting no strokes was defined as the date of the final MRI scan. The number of MRI scans ranged from two to eight (median, three) and the follow-up period ranged from 2 to 31 months (median, 15 mo).

Statistical Analysis

The data were analyzed with JMP software (version 6.0; SAS Institute Inc., Cary, NC). Patients were divided into three groups according to the number of MBs observed in the initial MRI scans: the non-MB group (no MBs present), single-MB group (only one MB present), and multi-MB group (multiple MBs present). The difference between the three groups in terms of clinical parameters was statistically evaluated. A difference in continuous variables was evaluated with analysis of variance followed by Tukey-Kramer's test; variables expressed as a proportion were estimated using the χ^2 test. The risk of subsequent cerebral hemorrhage and cerebral infarction was estimated by Kaplan-Meier analysis. The significance of group differences was assessed with the log-rank test. We also statistically evaluated the non-multi-MB group (comprising patients in the non-MB group and single-MB group) and the multi-MB group for differences in their clinical parameters. Differences in continuous variables were evaluated with the Wilcoxon test and variables expressed as proportions were estimated using the χ^2 test. In addition, multivariate analysis was performed with the Cox proportional hazard model. In all statistical analyses, we used a P value of less than 0.05 as the level of significance.

RESULTS

MBs in the Initial Study

Among the 50 patients enrolled in this study, MBs were found in 23 patients and not found in 27 patients in the initial MRI study (non-MB group). In the 23 patients with MBs, 11 patients had a single MB (single-MB group) and the remaining 12 patients had multiple MBs (multi-MB group). The number of MBs ranged from one to 18 (median, two) with a total of 66 MBs found in the 23 patients. Among these, 47 MBs (71.2%) were located in the periventricular white matter.

Subsequent Stroke during Follow-up

Four of the 50 patients exhibited subsequent hemorrhage during the follow-up period. Three of these cases occurred after bypass surgery in locations where MBs had been detected; two of the cases were fatal. Two of the four patients presented with previous intracerebral hemorrhage. Another three of the 50 patients exhibited subsequent ischemic strokes during the follow-up period. All ischemic strokes occurred before bypass surgery.

Differences in Clinical Parameters Among the Non-MB, Single-MB, and Multi-MB Groups

Of the 50 patients with MMD, 27 belonged to the non-MB group, 11 to the single-MB group, and 12 to the multi-MB group. The clinical characteristics of the patients in each group are shown in *Table 1*. Analysis of variance followed by Tukey-Kramer's test revealed that the mean age of patients in both the single-MB and multi-MB groups was significantly higher than that of patients in the non-MB group (*Table 1*). No other differences among the three groups were evident in either the clinical characteristics or follow-up periods.

TABLE 1. Differences in clinical parameters among the non-microbleed, single-microbleed, and multi-microbleed groups[a]

	Total (n = 50)	Non-MB group (n = 27)	Single-MB group (n = 11)	Multi-MB group (n = 12)	*P* value
Age, mean ± SD (yr)	40.5 ± 16.2	33.3 ± 14.1	49.1 ± 14.2	49.0 ± 15.3	0.0017[b]
Female, no. (%)	37 (74.0)	19 (70.4)	10 (90.9)	8 (66.7)	0.3405
Past vascular events					
TIA, no. (%)	31 (62.0)	17 (63.0)	7 (63.6)	7 (58.3)	0.9552
Cerebrovascular infarction, no. (%)	17 (34.0)	8 (29.6)	4 (36.3)	5 (41.7)	0.7514
Intracerebral hemorrhage, no. (%)	19 (38.0)	10 (37.1)	2 (18.2)	7 (58.3)	0.1388
Under antiplatelet medication, no. (%)	37 (74.0)	21 (77.8)	7 (63.6)	9 (75.0)	0.6635
Under antihypertensive medication, no. (%)	12 (24.0)	5 (18.5)	3 (27.3)	4 (33.3)	0.5820
Systolic blood pressure, mean ± SD (mmHg)	127.7 ± 18.0	125.8 ± 18.0	124.0 ± 17.7	135.3 ± 17.6	0.2360
Diastolic blood pressure, mean ± SD (mmHg)	75.6 ± 12.4	74.8 ± 14.9	75.2 ± 7.6	77.8 ± 10.2	0.7809
Completion of bypass surgery, no. (%)	23 (46.0)	12 (44.4)	5 (45.5)	6 (50.0)	0.9489
Follow-up period, mean ± SD (mo)	16.6 ± 8.8	16.2 ± 8.6	18.4 ± 8.7	15.8 ± 9.7	0.7420

[a] MB, microbleed; SD, standard deviation; TIA, transient ischemic attack.

[b] The difference between continuous variables was evaluated by analysis of variance followed by Tukey-Kramer's test; Tukey-Kramer's test indicates a significant difference between the non-MB and single-MB groups. Variables expressed as a proportion were estimated by the χ^2 test. No difference in the *P* value was seen between the two tests. One statistical difference among the three groups should be noted: the mean age of patients in both the single-MB group and multi-MB group was significantly higher than that of the non-MB group.

MBs and Subsequent Stroke

Kaplan-Meier curves of the three groups also showed a significantly higher likelihood of subsequent hemorrhage in the multi-MB group than in either the non-MB group or single-MB group (*Fig. 1A*). Kaplan-Meier curves of the three groups showed no significant differences between the subsequent infarction-free ratios of the three groups (*Fig. 1B*).

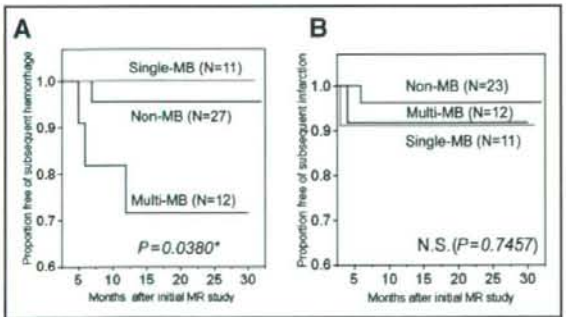

FIGURE 1. *Kaplan-Meier curves showing the subsequent hemorrhage-free ratios* (**A**) *and subsequent cerebral infarction-free ratios* (**B**) *in the non-microbleed (MB), single-MB, and multi-MB groups. The multi-MB group exhibited a significantly higher risk of subsequent hemorrhage than did the non-MB group and single-MB group (P = 0.0380)* (**A**). *No significant difference was seen in the risk of subsequent infarction among the three groups* (**B**). Asterisk, *significant difference (P < 0.05).* N.S., *no significant difference.*

Multivariate Analysis

The clinical parameters of the patients in the nonmulti-MB and multi-MB groups are shown in *Table 2*. The mean age of the patients in the multi-MB group was significantly higher than that of patients in the nonmulti-MB group (*Table 2*). No other differences in clinical characteristics or follow-up periods were evident between the two groups. Multivariate analysis using the Cox proportional hazard model demonstrated that the presence of multiple MBs adjusted by age was an independent risk factor for subsequent hemorrhage (hazard ratio, 2.891; 95% confidence interval, 1.001–13.24) (*Table 3*).

Bypass Surgery and Development of New MBs

Twenty-three patients in our series had received unilateral or bilateral revascularization before the initial MRI scans. The period between surgery and initial MRI scans ranged between 7 and 277 months (median, 160 mo); this was too long a period to allow evaluation of the effects of bypass surgery on the development of new MBs in those patients. Of the 13 patients who underwent postoperative MRI studies within 3 months of surgery, only one patient developed new MBs. This patient died of the subsequent intracerebral hemorrhage shown in *Figure 1*. None of the remaining 12 patients developed MBs after surgery.

Types of Onset Symptoms and Subsequent Hemorrhage

Among the 19 patients presenting with cerebral hemorrhage before the initial MRI scans, six exhibited ischemic onset. Although four patients developed new cerebral hemorrhages during the follow-up period, two had an ischemic episode. In total, cerebral hemorrhage with ischemic onset occurred in

TABLE 2. Differences in clinical parameters between the nonmulti-microbleed group (including non-microbleed and single-microbleed groups) and multi-microbleed group[a]

	Total (n = 50)	Nonmulti-MB group (n = 38)	Multi-MB group (n = 12)	*P* value
Age, mean ± SD (yr)	40.5 ± 16.2	37.9 ± 15.8	49.0 ± 15.3[b]	0.0336[c]
Female, no. (%)	37 (74.0)	29 (76.3)	8 (66.7)	0.5065
Past vascular events				
TIA, no. (%)	31 (62.0)	24 (63.2)	7 (58.3)	0.7640
Cerebral infarction, no. (%)	17 (34.0)	12 (31.6)	5 (41.7)	0.5202
Intracerebral hemorrhage, no. (%)	19 (38.0)	12 (31.6)	7 (58.3)	0.0960
Under antiplatelet medication, no. (%)	37 (74.0)	28 (73.7)	9 (75.0)	0.9278
Under antihypertensive medication, no. (%)	12 (24.0)	5 (18.5)	4 (33.3)	0.5820
Systolic blood pressure, mean ± SD (mmHg)	127.3 ± 18.3	124.3 ± 17.7	135.3 ± 17.7	0.0591
Diastolic blood pressure, mean ± SD (mmHg)	75.5 ± 12.7	74.9 ± 13.1	77.8 ± 10.2	0.3867
Completion of bypass surgery, no. (%)	23 (46.0)	17 (44.7)	6 (50.0)	0.7498
Follow-up period, mean ± SD (mo)	16.6 ± 8.8	16.8 ± 8.6	15.8 ± 9.7	0.7326

[a] MB, microbleed; SD, standard deviation; TIA, transient ischemic attack.
[b] Continuous variables were evaluated with the Wilcoxon test; variables expressed as a proportion were estimated with the χ^2 test. One statistical difference between the two groups should be noted: the mean age of patients in the multi-MB group was significantly higher than that of patients in the nonmulti-MB group.
[c] Significant difference ($P < 0.05$).

TABLE 3. Multivariate analysis with the Cox proportional hazard model revealed the presence of multiple microbleeds as an independent predictive factor[a]

	P value	Hazard ratio	95% confidence interval	
			Lower limit	Upper limit
Multiple microbleeds	0.0497[b]	2.89	1.001	13.24
Age	0.426	1.03	0.899	1.039

[a] Hazard ratio, 2.89; 95% confidence interval, 1.001–13.24.
[b] Significant difference ($P < 0.05$).

eight patients and cerebral hemorrhage with hemorrhagic onset occurred in 13 patients. The ischemic-onset group and hemorrhage-onset group exhibited no significant difference in the prevalence of hemorrhage.

Illustrative Cases

Patient 1

A 49-year-old man with MMD presented with a history of cerebral infarction and, on admission to our institute, recurrent transient attacks of left hemiparesis and left hemiparesthesia. He had received antihypertensive and antiplatelet medications before admission. T2*-weighted imaging performed on admission with a 3-T MRI unit revealed multiple asymptomatic MBs in the periventricular regions (*Fig. 2A*). After a diagnosis of ischemic MMD, STA-MCA anastomosis with EMS was performed on both hemispheres. He was discharged without neurological deficit. An MRI scan performed 1 month after surgery revealed the number and size of the MBs had increased with perifocal edema (*Fig. 2B*). Four months after surgery (5 mo after the initial MRI scan), fatal intracerebral hemorrhage with intraventricular perforation occurred in the region where enlargement of the MBs had been detected (*Fig. 2C*).

Patient 2

A 49-year-old woman with MMD presented with a history of intracerebral hemorrhage in the right temporal lobe (*Fig. 3, A* and *B*). Unsuccessful direct bypass surgery was performed on the right side. Subsequently, the patient presented with frequent transient attacks of bilateral motor weakness and was admitted to our institution. On admission, a T2*-weighted imaging study was performed with a 3-T MRI unit, revealing multiple asymptomatic MBs in the head of the right caudate putamen that were not contiguous with the previous hematoma (*Fig. 3, C* and *D*). Recurrent intracranial hemorrhage occurred 6 months after the surgery. The hematoma had apparently originated from the site where the MRI scan had revealed the MBs (*Fig. 3, E* and *F*).

DISCUSSION

The mortality rate for cerebral hemorrhage in MMD is 20%, and cerebral hemorrhage is the largest risk factor contributing to the poor prognosis with this entity (26, 33). Recurrent cerebral hemorrhage occurs in 33 to 66% of patients with hemorrhagic onset (42, 57) and hemorrhage occurs in 10 to 20% after revascularization surgery in patients with ischemic onset (14, 46). However, the exact mechanism of hemorrhage remains unknown and no preventive treatment has been devised (1, 14, 20, 40, 42). Our study suggests that the presence of multiple MBs detected with T2*-weighted MRI scans can be regarded as a predictor for cerebral hemorrhage in patients with MMD.

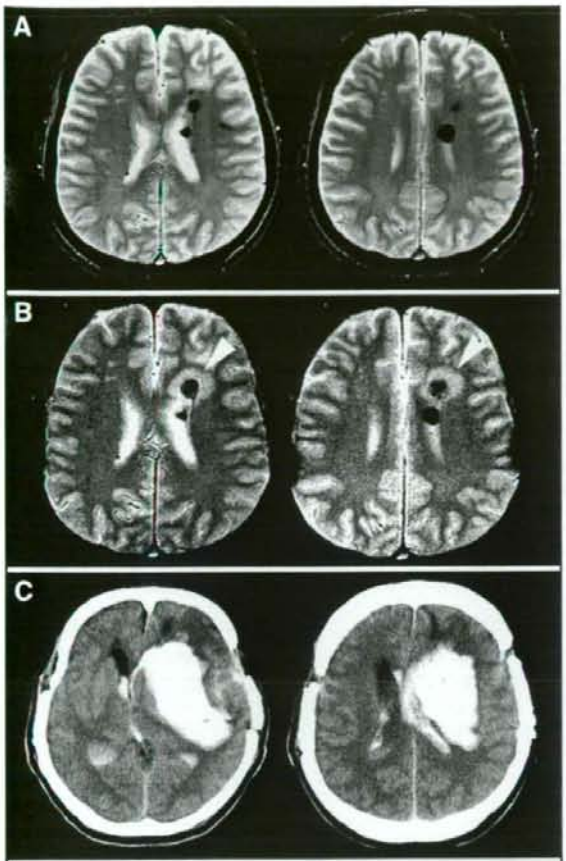

FIGURE 2. *Magnetic resonance imaging (MRI) scans demonstrating sequential changes in MBs transforming into symptomatic hemorrhages.* **A**, *in a 49-year-old man with ischemic moyamoya disease* (MMD), *multiple MBs were revealed in the initial 3-T MRI study. Superficial temporal artery-to-middle cerebral artery (STA-MCA) anastomosis with encephalomyosynangiosis was performed on both hemispheres. One month after completion of the surgery, the number and size of the MBs increased with perifocal edema* (**B**, arrowhead). **C**, *4 months after surgery (5 mo after the initial MRI study), fatal intracerebral hemorrhage (ICH) occurred with intraventricular perforation around the region in which enlarged MBs were demonstrated.*

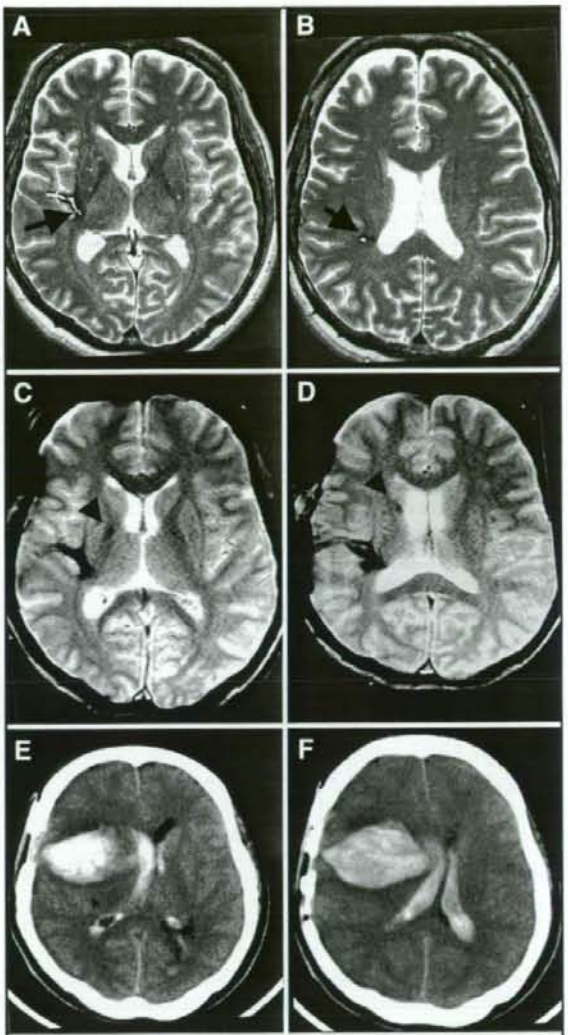

FIGURE 3. **A** *and* **B**, *another case of MBs exhibited subsequent symptomatic hemorrhage. A 49-year-old woman with MMD had a history of previous ICH in the right temporal lobe.* Arrows *indicate MBs;* asterisks *indicate previous hematoma. Unsuccessful direct bypass surgery was performed on the right side. Subsequently, the patient presented with frequent transient attacks of bilateral motor weakness and was admitted to our institute.* **C** *and* **D**, *on admission, a T2*-weighted imaging study was performed with a 3-T MRI unit revealing multiple asymptomatic MBs in the right caudate putamen that were not contiguous with the previous hematoma* (arrowheads). *Recurrent ICH occurred 6 months after surgery. However, recurrent ICH occurred on the day of discharge.* **E** *and* **F**, *the hematoma had apparently originated not from the site of the previous hemorrhage, but from the site where the MBs had been revealed.*

MBs were first described as small, rounded, foci-appearing hypointense on T2*-weighted images (8, 11, 45). Numerous reports have investigated the prevalence of MBs in healthy individuals and in patients with various cerebral angiopathies (55). The incidence of MBs is 3.1% in healthy Japanese adults, which correlates with hypertension and smoking (52). The Austrian Stroke Prevention study reported the incidence as 6.4% (47). The Framingham study reported the overall prevalence of MBs in healthy individuals as 4.7% (21). Age and sex are predictors

of MBs (21). Thus, the incidence of MBs in healthy individuals is believed to range between 3.1 and 6.4%. In hypertensive patients, the incidence increases to 56% (36). In patients with ischemic cerebrovascular disease, the prevalence of MBs ranges between 16 and 68% (6, 25, 31, 35, 36, 43, 53). In patients with intracerebral hemorrhage, the incidence ranges between 54 and 70%, which is 10 times greater than that of healthy individuals (22, 25, 31, 36, 37, 44, 48, 53). In patients with cerebral amyloid angiopathy (CAA) and cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy, the incidence ranges between 63 and 73% (3, 12, 13, 32, 49) and between 25 and 69% (5, 38, 54), respectively. We previously reported the incidence of MBs in patients with MMD as 44% in a 3-T MRI study (29), whereas other investigators have reported the incidence as 14.8% in a 1.5-T MRI study (19); these rates are significantly higher than those for healthy individuals.

Several prospective studies have revealed that the presence of MBs appears to be a risk factor for subsequent strokes or cerebral hemorrhage after ischemic stroke (2, 7, 16); for major symptomatic hemorrhage after intraarterial thrombolytic therapy (28, 30); and for recurrent hemorrhage in CAA (49). Therefore, MBs have been considered a general marker of vascular vulnerability in various types of bleeding-prone cerebral angiopathy (55). Fan et al. (7) performed a prospective analysis of 121 patients with acute cerebral infarction within a follow-up period of 27 months, revealing a significantly higher incidence of subsequent intracerebral hemorrhage (ICH) in patients with MBs than in patients without MBs. Boulanger et al. (2) performed a prospective study of 236 patients with acute ischemic stroke or transient ischemic attack and demonstrated that disability or fatal stroke resulted more frequently in patients with MBs than in patients without MBs within a follow-up period of 18 months. Imaizumi et al. (16) performed an excellent prospective study of 337 patients with small vessel diseases (SVDs) such as lacunar infarction and primary ICH. They reported that the incidence of lacunar stroke and ICH in the follow-up period correlated with the presence of more than five MBs and a history of ICH. Recently, the clinical significance of MBs has been best clarified in CAA. The number of existing MBs and the number of new developing MBs increased the risk of recurrent hemorrhage in patients with CAA (49). These observations suggest that the presence of MBs, especially multiple MBs, can be a predictor of subsequent stroke.

In this study, only the presence of multiple MBs seemed to be a predictor for subsequent hemorrhage in patients with MMD. In contrast, our study did not show MBs to be a predictor of subsequent infarction in patients with MMD. This might be caused by the difference between patients with MMD and patients with SVDs such as lacunar stroke and primary ICH in terms of the mechanism causing ischemic stroke because ischemic stroke is not caused by SVDs but rather mainly by hemodynamic deficiency in patients with MMD (15, 51). Thus, bypass surgery is effective at preventing ischemic stroke in patients with MMD (4, 15, 24, 40), and 46% of patients in this series underwent surgery before the initial MRI study.

The radiological character of MBs in patients with MMD was somewhat different from that of patients with SVDs (34, 55). It is more common to see a large number of MBs in patients with SVDs than in patients with MMD (35). In this series, 46% of the patients had MBs, but the median number of MBs in those patients was only two. Although MBs are usually located in both the basal ganglia and subcortical regions in patients with SVDs (27, 34, 55), MBs in patients with MMD are located mainly in the periventricular white matter. Development and dilatation of the arteries situated in the paraventricular white matter such as choroidal arteries and branches of posterior communicating arteries have been reported as risk factors for hemorrhage (14, 17, 41). MBs might be related to these risk factors. An age between 46 and 50 has also been reported as a risk factor for recurrent hemorrhage (42). In this study, patients with MBs were older than the patients without MBs; however, multivariate analysis revealed that the presence of multiple MBs was an independent risk factor for hemorrhage.

In this study, the development of new MBs after bypass surgery was observed in only one patient; thus, the development of new MBs related to bypass surgery seemed rare. Generally, bypass surgery has been thought to prevent cerebral infarction in MMD (18, 23, 24). Indeed, no ischemic strokes occurred during the follow-up period after completion of bypass. In contrast, three of the four hemorrhagic strokes during the follow-up period occurred after bypass. The prophylactic effect of bypass surgery against cerebral hemorrhage remains uncertain, and this issue will be clarified by a prospective, randomized trial in Japan (Japan Adult Moyamoya Trial) (39). Although this series included eight patients with ischemic onset who exhibited delayed hemorrhage, the occurrence ratio of hemorrhage in patients with ischemic onset did not differ much from that in patients without ischemic episodes. Thus, the relationship between progressive ischemia and the occurrence of hemorrhage also remains uncertain.

Our study showed that the presence of multiple MBs might indicate risk of subsequent hemorrhage in MMD. In addition, like with CAA (49), the development of new MBs might be another risk factor for subsequent hemorrhage. This raises the question of how to manage new MBs revealed to be developing in patients with MMD. We can suggest no answer except for observation of such MBs with close follow-up with MRI scans. We currently perform monthly MRI scans to determine whether or not such MBs are progressing. The risk of antiplatelet therapy in patients with MBs has been examined in only two retrospective studies (55, 56). One study suggested an increased risk of hemorrhage from antiplatelet therapy (56), whereas the other showed that MBs did not alter the risk (55). The risk of anticoagulation and antiplatelet therapy in patients with MBs should be investigated through further prospective studies.

MMD is also rare in Japan (7); our study, therefore, has insufficient statistical significance because of the small number of patients and short follow-up period. These limitations should be noted in the interpretation of our results. Further study with a larger number of patients and a longer follow-up period is

required to confirm the results. At minimum, however, our study strongly suggests that the presence of multiple MBs in patients with MMD indicates an increased risk of hemorrhage. The mortality rate for cerebral hemorrhage in MMD remains quite high, whereas MRI scans for detecting MBs can be performed less invasively; thus, our data are believed to be of clinical importance.

CONCLUSION

In summary, the presence of multiple MBs in patients with MMD might be an independent predictor of subsequent hemorrhage. A study with a larger number of patients and a longer follow-up period is required to confirm the results.

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COMMENTS

Kikuta et al. examine the relationship between asymptomatic microbleeds (MBs) and the occurrence of subsequent stroke in patients with moyamoya disease. This prospective study included 50 consecutive patients and used 3-T magnetic resonance imaging (MRI). Follow-up occurred from the date of the initial MRI study until the date of the first subsequent stroke or final MRI study, with a median period of 15 months. Results showed a significantly higher likelihood of subsequent hemorrhage in patients with multiple MBs compared to those without MBs or with single events only. The authors concluded that, not surprisingly, prior MBs are predictive of future hemorrhagic events secondary to moyamoya disease.

Operative intervention for patients with moyamoya disease consists of bypass surgery, with appropriate patient selection remaining controversial. In this study, the development of new MBs after bypass surgery was observed in only one patient. In addition, no ischemic strokes occurred during follow-up after completion of the bypass. In contrast, three of the four hemorrhagic strokes during follow-up occurred after bypass. Because bypass surgery is primarily used to prevent cerebral infarction secondary to ischemic stroke, the prophylactic effect of bypass surgery against cerebral hemorrhage remains uncertain. We hope that this issue will be clarified by the ongoing Japanese adult moyamoya trial (1).

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1. Miyamoto S; Japan Adult Moyamoya Trial Group: Study design for a prospective randomized trial of extracranial-intracranial bypass surgery for adults with moyamoya disease and hemorrhagic onset. **Neurol Med Chir (Tokyo)** 44:218–219, 2004.

Kikuta et al. examine 50 consecutive patients with moyamoya disease enrolled in a prospective study in which MRI studies were obtained and the patients were followed clinically. In 27 patients, there were no MBs identified, whereas 66 areas of MBs were identified in the remaining 23 patients. Eleven patients had a single area of abnormality, and 12 patients had multiple areas. In evaluation of these patients, the authors identified a significantly higher incidence of hemorrhage in the patients with MBs. As the authors themselves point out, MRI scans identify increased areas of MBs in several other disease states, including hypertension, amyloid angiopathy, intracerebral hemorrhage, and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

The big issue is whether the presence of MBs in a patient with moyamoya disease would alter the direction of therapy. Encephaloduroarteriosynangiosis procedures and extracranial-intracranial bypass procedures for moyamoya disease are designed to minimize or eliminate ischemic events. Whether or not these procedures decrease the incidence of subsequent hemorrhage remains open to discussion.

Certainly, Kikuta et al. have identified a subpopulation of patients with moyamoya disease at higher risk for hemorrhage. A critical issue to study in the future is whether any therapeutic intervention can target these patients in a way that will minimize the subsequent hemorrhage rate.

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Kikuta et al. present their study on the presence of multiple MBs as a predictive factor of subsequent cerebral hemorrhage in patients with moyamoya disease. A consecutive series of 50 patients was studied for the presence of MBs seen on T2* imaging acquired on 3-T MRI. In this study, MBs were present in 46% of patients; this is in agreement with the authors' earlier published data, where MBs were identified in 44% of patients with moyamoya disease and 5.8% of healthy control individuals. The authors identified that patients who had multiple MBs were more likely to experience a hemorrhagic stroke in a mean follow-up period of 50 months as compared with patients who harbored a single MB or no MB. Age was significantly higher in the single-MB and multi-MB groups compared with the non-MB group and also higher in the multi-MB group compared with the combined non-multi-MB group. However, age-adjusted analysis using the Cox proportional hazard model showed that the presence of multiple MBs was an independent risk factor for subsequent intracerebral hemorrhage in patients with moyamoya disease.

This is an interesting, clearly structured study of moyamoya patients with a finding that is potentially relevant for clinical decision making. Although it is not definitely proven that cerebral revascularization of moyamoya patients decreases the risk of future hemorrhage, this study suggests that patients with multiple MBs should be closely followed, avoid excessive hypertension, and possibly consider early revascularization.

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Kikuta et al. conducted a prospective study aimed at examining the relationship between asymptomatic MBs as detected by MRI and subsequent intracerebral hemorrhage in patients with moyamoya disease. Fifty patients with an established diagnosis were followed with a serial MRI study. MBs were identified in the initial scan of 23 patients, 11 of whom had single MBs and 12 of whom had multiple MBs. Interestingly, the MBs were present in the periventricular white mater and not in the basal ganglia. The rate of hemorrhagic stroke was significantly higher in the subgroup of patients with multiple MBs.

The hemorrhagic complication in moyamoya disease is devastating, and as mentioned by the authors, is the main factor contributing to the poor prognosis of patients with this entity. Although this study by Kikuta et al. may not change the therapeutic strategies that are presently used to treat patients with moyamoya disease, it does increase current knowledge. New preventive measures for hemorrhagic events should be the next step in the research effort.

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Moyamoya disease: current concepts and future perspectives

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Moyamoya disease is an uncommon cerebrovascular disease that is characterised by progressive stenosis of the terminal portion of the internal carotid artery and its main branches. The disease is associated with the development of dilated, fragile collateral vessels at the base of the brain, which are termed moyamoya vessels. The incidence of moyamoya disease is high in east Asia, and familial forms account for about 15% of patients with this disease. Moyamoya disease has several unique clinical features, which include two peaks of age distribution at 5 years and at about 40 years. Most paediatric patients have ischaemic attacks, whereas adult patients can have ischaemic attacks, intracranial bleeding, or both. Extracranial–intracranial arterial bypass, including anastomosis of the superficial temporal artery to the middle cerebral artery and indirect bypass, can help prevent further ischaemic attacks, although the beneficial effect on haemorrhagic stroke is still not clear. In this Review, we summarise the epidemiology, aetiology, clinical features, diagnosis, surgical treatment, and outcomes of moyamoya disease. Recent updates and future perspectives for moyamoya disease will also be discussed.

Introduction

Moyamoya disease is an uncommon cerebrovascular disorder that is characterised by progressive occlusion of the supraclinoid internal carotid artery (ICA) and its main branches within the circle of Willis. This occlusion results in the formation of a fine vascular network (the moyamoya vessels) at the base of the brain. The appearance of this vascular network on an angiogram looks like a puff of cigarette smoke drifting in the air (figure 1); thus, in 1969, Suzuki and Takaku[1] named this novel disorder "moyamoya disease", because "moyamoya" means "puff of smoke" in Japanese. The predominant feature of the pathology of moyamoya disease is now known to be progressive stenosis of the carotid artery terminations, and the moyamoya vessels are the dilated perforating arteries that function as collateral pathways.[2] Recent studies have rapidly expanded our knowledge of the basic and clinical aspects of moyamoya disease, including the aetiology, pathophysiology, surgical treatment, and long-term prognosis of the disorder; however, further understanding of the pathophysiology, diagnosis, and treatments of this disease is needed to improve the long-term outcome for these patients. In this Review, we describe current knowledge and discuss future perspectives on moyamoya disease aimed at improving the outcomes for patients with this disorder.

Definition

In 1997, the Research Committee on Spontaneous Occlusion of the Circle of Willis (Moyamoya Disease) published guidelines for the diagnosis of moyamoya disease in English.[2] According to these guidelines, moyamoya disease is characterised by stenosis or occlusion at the terminal portions of the ICA or the proximal areas of the anterior or the middle cerebral arteries (ACAs, MCAs) and abnormal vascular networks in the arterial territories near the occlusive or stenotic lesions, as shown by cerebral angiography. Definite cases of moyamoya disease are diagnosed in patients with bilateral lesions (figure 1), whereas patients with unilateral lesions are diagnosed as probable cases. Because the aetiology of moyamoya disease is unknown, so-called quasi-moyamoya diseases or moyamoya syndromes—ie, conditions such as cerebrovascular disease with atherosclerosis, autoimmune disease, meningitis, brain neoplasm, Down's syndrome, neurofibromatosis, head trauma, or irradiation to the head, as well as other conditions—need to be eliminated.

Epidemiology

The incidence of moyamoya disease is high in countries in east Asia, such as Japan and Korea. In Japan, the annual prevalence and incidence have been estimated at 3·16 and 0·35 per 100000, respectively. The female to male

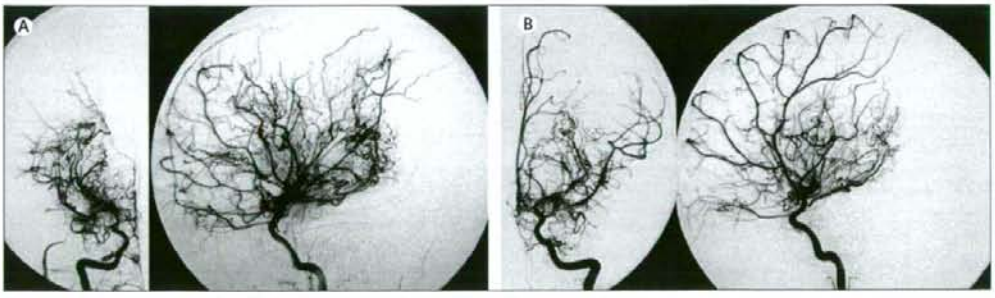

Figure 1: **Typical findings seen with cerebral angiography in an 8-year-old boy with moyamoya disease**
(A) Angiogram of the right internal carotid artery. (B) Angiogram of the left internal carotid artery.

ratio was shown to be 1·8, and the distribution of age at onset has been suggested to have two peaks: one at 5 years of age and one lower peak at about 40 years of age.[3] However, an all-inclusive survey done in Hokkaido, one of the main islands of Japan, has shown different results.[4] In this study, the annual prevalence and incidence of moyamoya disease were shown to be higher than in previous studies: 10·5 and 0·94 per 100 000, respectively. The female to male ratio was also different (2·18). Although two distribution peaks for age at onset were still seen, the highest peak was between 45 and 49 years of age, and the second peak was between 5 and 9 years of age.[4] There are several explanations for the discrepancy between these two studies. First, the survey methods are different among reports. Most epidemiological studies were based on data obtained from questionnaire surveys in hospitals with many patients, whereas the Hokkaido study was a survey of all patients who were diagnosed with moyamoya disease in Hokkaido (which has a population of about 5·6 million) over a specific time period.[4] Second, although the incidence of asymptomatic moyamoya disease was, until recently, thought to be low,[5] widespread use of non-invasive MRI might increase the detection of asymptomatic moyamoya disease in adults. Finally, the epidemiological features in moyamoya disease might gradually change over time; for example, for reasons not yet understood, the incidence of paediatric moyamoya disease seems to have started to decrease.

Goto and Yonekawa[6] collected published data from 1063 patients with moyamoya disease from countries other than Japan, and found that 625 patients were from Asia, 201 were from Europe, 176 were from North America and South America, 52 were from Africa, and nine were from Australia. Numaguchi and co-workers[7] identified the ethnic origins of 54 patients with moyamoya disease in the USA, and found that 35 patients were white, eight were Asians, five were African Americans, three were Haitians, and three were Hispanics. However, in an analysis of the epidemiological features of this disease in Hawaii, where a high proportion of the population are Asian and Pacific Islanders (56%), Graham and Matoba[8] found that the incidence and prevalence of moyamoya disease were higher than in the rest of the USA because of the larger percentage of people with Asian ethnic origins. These authors suggested that genetic, rather than environmental, factors explained the higher incidence of moyamoya disease in Hawaii. Uchino and co-workers[9] collected data from 298 patients with moyamoya disease in California and Washington between 1987 and 1998 and found the incidence to be 0·086 per 100 000, which is lower than that in Japan. The incidence rate ratios of specific ethnic origins compared with whites were 4·6 for Asian Americans, 2·2 for African Americans, and 0·5 for Hispanics. The incidence in Europe has been shown to be about 10% of that in Japan.[10]

An epidemiological feature of moyamoya disease is the high incidence of familial occurrence, which accounts for about 15% of patients.[11] 172 familial cases in 76 pedigrees have been reported; of these, 38 parent-offspring pairs in 16 pedigrees and 128 sibling pairs in 51 pedigrees have been described.[12,13] Epidemiological analyses have shown distinctive features of familial moyamoya disease: the ratio of women to men was 5·0 in familial cases, but 1·6 in sporadic cases; the mean (SD) age of onset was 11·8 (11·7) years in familial cases but 30·0 (20·9) years in sporadic cases. Of eight parent-offspring pairs, all were mother-offspring pairs. The parents presented with symptoms of moyamoya disease at 22–36 years of age (mean 30·7 [7·5] years), whereas their offspring presented with symptoms at 5–11 years of age (mean 7·2 [2·7] years), which suggests a strong association with anticipation in familial moyamoya disease.[11]

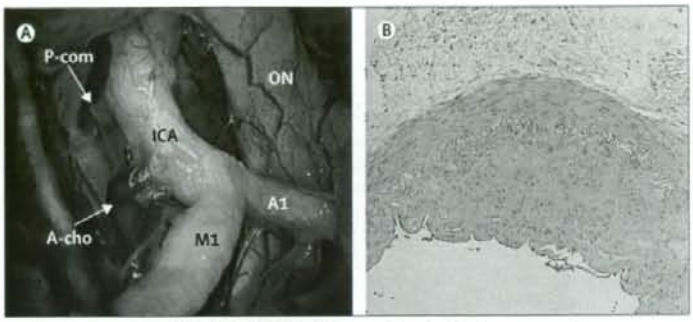

Figure 2: **Intraoperative and histological findings of the carotid termination in moyamoya disease**
(A) Intraoperative photograph of the carotid terminations in a 60-year-old man with moyamoya disease. A substantial decrease in the outer diameter of the ICA and the horizontal portions of the middle cerebral artery (M1) and anterior cerebral artery (A1) are noticeable. The sizes of the P-com, A-cho, and the perforators from the A1 are normal. (B) Haematoxylin and eosin staining of the terminal portion of the ICA in a 30-year-old woman who developed fatal intracranial haemorrhage owing to moyamoya disease. Note the thickening of the intima, irregular undulation of the internal elastic lamina, and the attenuation of the media. Original magnification ×100. A1=segment of the anterior cerebral artery. A-cho=anterior choroidal artery. ICA=internal carotid artery. M1=segment of the middle cerebral artery. ON=optic nerve. P-com=posterior communicating artery.

Pathophysiology and aetiology

Intraoperative and pathological observations have shown that the outer diameters of the relevant carotid artery terminations are markedly diminished in moyamoya disease. In addition, histopathological findings in the carotid terminations have shown fibrocellular thickening of the intima, an irregular undulation (waving) of the internal elastic lamina, and attenuation of the media (figure 2).[14] Data from recent studies have suggested that caspase-3-dependent apoptosis might be associated with these histopathological changes.[15,16] Moyamoya vessels are the dilated perforating arteries that have various histopathological changes, including fibrin deposits in the wall, fragmented elastic laminae, attenuated media, and the formation of microaneurysms. Collapse of the artery lumen and subsequent thrombosis can also be seen in the moyamoya vessels;[17,18] therefore, these histopathological changes might be closely associated with the onset of ischaemic and haemorrhagic stroke.

Results from previous studies have shown that concentrations of certain growth factors or cytokines are increased in the CSF of patients with moyamoya disease. The expression of basic fibroblast growth factor is increased in the CSF and in the intracranial and extracranial arteries.[15,19–22] Concentrations of soluble vascular-cell adhesion molecule type 1, intercellular adhesion molecule type 1, and E-selectin in the CSF are also increased in moyamoya disease, which suggests an inflammatory process in the CNS.[23] Cellular retinoic-acid-binding protein I has also been identified from the CSF of patients with moyamoya disease.[24] Furthermore, we have recently shown that the concentrations of hepatocyte growth factor in the CSF are substantially higher in patients with moyamoya disease than in patients with occlusion of the ICA (820·3±319·0 pg/mL *vs* 443·2±193·5 pg/mL; p<0·001).[25] In this study, hepatocyte growth factor and its receptor c-Met were widely expressed in the media and in the thickened intima of the carotid terminations in patients with moyamoya disease, but not in the control groups (patients with ICA occlusion or with cervical spondylosis). These findings suggest that enhanced expression of hepatocyte growth factor in the vascular smooth muscle cells might promote thickening of the intima and encourage migration of these muscle cells into the intima of the carotid terminations in patients with moyamoya disease.[25] Furthermore, these angiogenic proteins might have a role in the formation of collateral circulation after surgical revascularisation with indirect bypass.

The pathogenesis of moyamoya disease is still unclear.[26–33] No specific infectious pathogens have been identified, although data from epidemiological studies have indicated that infection in the head and neck might be implicated in the development of moyamoya disease.[27] Some researchers believe that genetic factors might also contribute to the development of the disease; data from an epidemiological study of familial moyamoya disease have suggested that moyamoya disease is probably inherited in a polygenic or autosomal dominant mode with a low penetrance.[28] Microsatellite linkage analysis has identified genetic loci that are associated with moyamoya disease on chromosomes 3, 6, 8, and 17.[29–32] However, the relevant genes have not been identified so far.[33]

Clinical presentations

The clinical features of moyamoya disease differ substantially between children and adults. Most children with moyamoya disease develop transient ischaemic attack (TIA) or cerebral infarction,[34] whereas about half of adult patients develop intracranial bleeding, and half develop TIA or cerebral infarction, or both.[34]

Transient ischaemic attack and ischaemic stroke

Moyamoya disease usually causes some cerebral ischaemia in the territory of the ICA, particularly in the frontal lobe. Therefore, most patients with moyamoya disease present with focal neurological signs, such as dysarthria, aphasia, or hemiparesis. However, moyamoya disease might also cause other atypical symptoms such as syncope, paraparesis, visual symptoms, or involuntary movements, particularly in children.[34–36] Some paediatric patients develop intellectual impairment owing to frontal lobe ischaemia, infarct, or both.[37,38] In rare cases, adult patients can develop cognitive dysfunction, such as short-term memory disturbance, irritability, or agitation; patients who present with these symptoms are commonly misdiagnosed with psychiatric disorders, such as schizophrenia, depression, or personality disorder.[39,40]

In paediatric patients, ischaemic attacks are characteristically induced by hyperventilation, for example when crying or playing a wind instrument. EEGs in paediatric patients with moyamoya disease are distinctive. In healthy children, hyperventilation generates high-amplitude slow waves, which disappear after hyperventilation stops (an event known as build up). However, in children with moyamoya disease, the slow waves reappear. Paediatric patients sometimes develop TIA when waves reappear while having EEG scans. This reappearance of the slow waves is pathognomonic for children with moyamoya disease, and is known as re-build up.[41] Recent observations suggest that this re-build up is triggered by post-hyperventilation hypoxia combined with a hyperventilation-induced reduction in blood flow, and originates in the deep cortical sulci, where the cerebral perfusion reserve is impaired.[42–47] Re-build up can completely disappear after effective surgical revascularisation.[46]

Intracranial bleeding

About half of adult patients with moyamoya disease develop intracranial bleeding.[34] There are two main causes of intracranial bleeding in moyamoya disease: rupture of dilated, fragile moyamoya vessels or rupture of saccular aneurysms in the circle of Willis. For the first, the rupture is due to persistent haemodynamic stress of the moyamoya vessels and occurs in the basal ganglia, thalamus, or periventricular region. Intraventricular haemorrhage is frequently complicated.[48,49] Peripheral aneurysms in the collateral vessels or moyamoya vessels might be identified on cerebral angiography in some patients.[50,51] For the second, rupture of saccular aneurysms located around the circle of Willis occurs most commonly at the basilar artery bifurcation or the junction of the basilar artery and the superior cerebellar artery. The vertebrobasilar system has an important role in providing collateral circulation in patients with moyamoya disease. Thus, haemodynamic stress probably induces the formation of a saccular aneurysm in the vertebrobasilar system; rupture of a saccular aneurysm causes subarachnoid haemorrhage.[50] There is increasing evidence that moyamoya disease in adults might induce subarachnoid haemorrhage over the cerebral cortex despite the absence of an intracranial aneurysm.[52–54] A third cause of intracranial bleeding in adult patients with moyamoya disease is therefore

rupture of the dilated collateral arteries on the brain surface, although this is rare.[54]

Pregnancy and childbirth might increase the risk of ischaemic or haemorrhagic stroke in women who are treated either medically or surgically for moyamoya disease. In particular, haemorrhagic stroke during pregnancy or birth commonly leads to poor functional outcome of the mother, as measured by the Glasgow outcome scale or modified Rankin scale.[55] In Japan, there are ongoing discussions about how to determine the optimal management for a safe pregnancy and birth for patients who have previously had surgical revascularisation.

Other neurological symptoms

Headache is one of the serious symptoms associated with moyamoya disease, particularly in paediatric patients, although there are only a few relevant articles that have been written in English. Patients typically present with frontal or migraine-like headache.[56] Seol and co-workers[56] assessed the clinical records of 204 children with moyamoya disease, and found that about 25% of patients complained of headache, and more than half of them still had headache for 12 months or longer after indirect bypass surgery. However, headache might occur after surgery in some paediatric patients who did not have preoperative headache.[56] In addition, epilepsy and involuntary movements are important clinical presentations in moyamoya disease: involuntary movements are mostly seen in paediatric patients.[36,57]

Diagnosis

A range of neurological disorders can lead to ischaemic or haemorrhagic stroke in children and adults with moyamoya disease. Therefore, precise analysis of radiological findings is important to make an accurate diagnosis, predict outcome, and determine appropriate therapeutic strategies for the patient.

Cerebral angiography

Cerebral angiography is still the gold standard for the diagnosis of moyamoya disease. Cerebral angiographs typically show stenosis or occlusion of the terminal part of the ICA (the C1–C2 portion) and the proximal part of the ACAs and MCAs bilaterally (figure 1). Stenosis or occlusion of the proximal part of the posterior cerebral artery also affects about 25% of patients with moyamoya disease.[35,58,59] The six-stage classification of the findings of cerebral angiography by Suzuki and Takaku[1] is well known and is widely used. Moyamoya disease is characterised by the extensive development of pathognomonic collateral pathways in response to changes due to progressive stenosis of the termini of the carotid artery.[1] The first pathway is known as "basal moyamoya" and includes abnormal dilation of the perforating arteries, such as the lenticulo-striate artery and the thalamo-perforating artery, in the basal ganglia and thalamus. The second pathway involves substantial dilation of the anterior choroidal and posterior pericallosal arteries, which provide collateral circulation in most patients with moyamoya disease. The third pathway, known as "ethmoidal moyamoya", involves dilation of the anterior and posterior ethmoidal arteries, which also function as collateral pathways, mainly from the ophthalmic arteries to the ACA branches. Finally, moyamoya disease often causes an abnormal vascular network at the cranial vault that supplies collateral flow from the dural arteries to pial arteries. This collateral pathway is known as "vault moyamoya" and is commonly observed in patients with advanced disease.

Cerebral angiography is useful to assess the development of collateral pathways through direct bypass, indirect bypass, or both. Effective bypass surgery leads to the disappearance or regression of moyamoya vessels because they are no longer required to function as collateral pathways. Postoperative angiography should take place at least 3 months after surgery because collateral pathways require 3–4 months to develop after indirect bypass surgery (see below).[60,61]

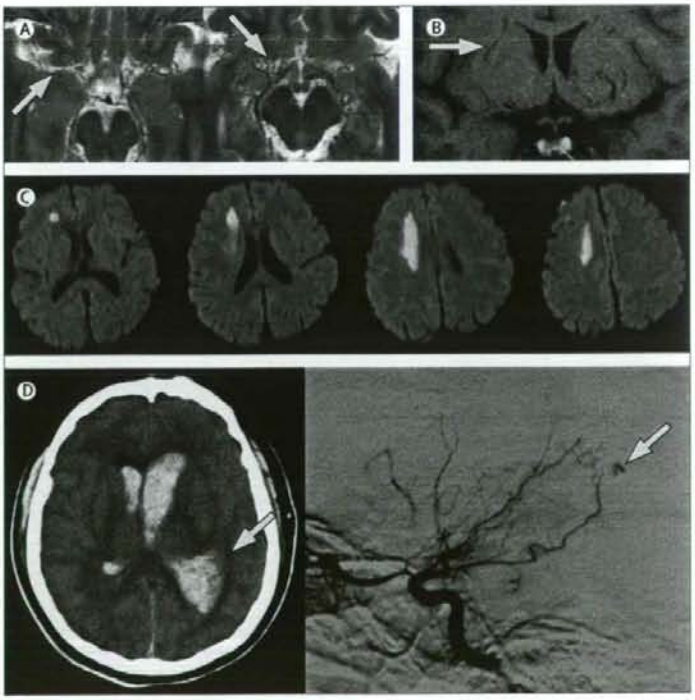

Figure 3: **Typical findings of moyamoya disease seen with MRI and CT**
(A) T2-weighted MRI of a 56-year-old woman that shows the disappearance of the flow void signal of the horizontal portion of the middle cerebral artery (left panel) and many small flow void signals in the basal cistern (right panel). (B) T1-weighted MRI of a 10-year-old boy shows the dilated basal moyamoya vessels in the basal ganglia (arrow). (C) Diffusion-weighted MRI of a 28-year-old man shows acute ischaemic damage in the right frontal lobe. (D) Plain CT scan of a 27-year-old man shows massive intraventricular haematoma associated with intracerebral haematoma adjacent to the left trigon (left panel). Left internal carotid angiogram shows a small aneurysm in the distal portion of the dilated anterior choroidal artery (right panel).

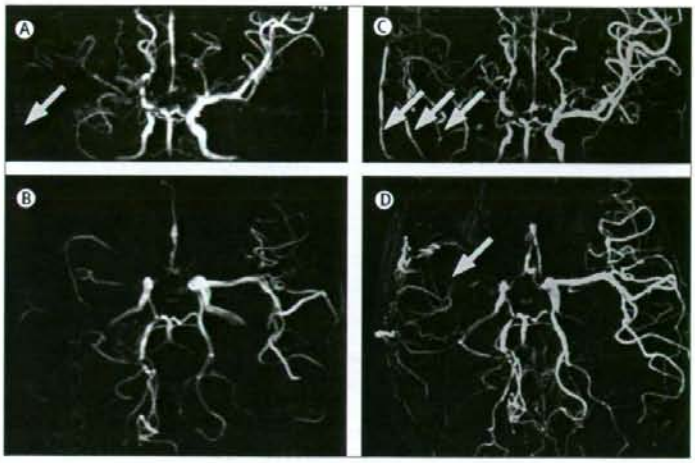

Figure 4: **Preoperative and postoperative MRA of a 40-year-old man with left hemiparesis**
Coronal (A) and axial views (B) of MRA before surgery show a marked stenosis of the right carotid terminations and a mild stenosis of the left anterior cerebral artery. A substantial decrease in flow signals of the branches of the right MCA can be seen. The calibre of the right STA is small (A; arrow). Coronal (C) and axial views (D) of MRA 4 months after STA–MCA anastomosis and encephaloduromyoarteriopericranial synangiosis show marked increase in the calibres of the right STA, deep temporal artery, and middle meningeal artery (C; arrows). Note a substantial increase in flow signals in the branches of the right MCA.

MRI and magnetic resonance angiography

MRI, including T2-weighted and fluid-attenuated inversion recovery (FLAIR) imaging, is useful to localise ischaemic and haemorrhagic lesions in the brain parenchyma. Diffusion-weighted MRI can be used to locate tissue damage in the acute stage of ischaemic stroke (<1 h). T2-weighted MRI is also useful to identify occlusive lesions around the circle of Willis and dilated moyamoya vessels.[62,63] T1-weighted MRI can be used to identify dilated moyamoya vessels in the basal ganglia and thalamus (figure 3). Asymptomatic microbleeds can be detected in about 15–44% of adult patients with T2*-weighted MRI.[64,65] Although the clinical importance of microbleeds has not yet been determined, these microbleeds might be an important predictor for subsequent haemorrhagic stroke in patients with moyamoya disease.[66,67]

Magnetic resonance angiography (MRA) is also useful to diagnose moyamoya disease in a non-invasive way. MRA can be used to identify stenotic lesions in the ends of the carotid artery; thus, MRA has enabled easier detection of asymptomatic patients with familial moyamoya disease.[68] However, the possibility of overestimation of accuracy should always be taken into account because of the imaging quality.[68,69] MRA can also can be used to identify moyamoya vessels around the basal ganglia and thalamus (figure 4).[69] In accordance with the guidelines of the Research Committee on Spontaneous Occlusion of the Circle of Willis (Moyamoya Disease), cerebral angiography is not mandatory if MRI and MRA show all of the following findings: stenosis or occlusion at the end of the ICA or at the proximal part of the ACAs and MCAs on MRA, and an abnormal vascular network seen in the basal ganglia with MRA; an abnormal vascular network that is evident from ipsilateral flow voids seen in the basal ganglia with MRI; and bilateral presentation of the above two findings.[2] However, the quality of MRA largely depends on the strength of the static magnetic field. The new criteria of the Research Committee for Diagnosis of Moyamoya Disease recommend MRA with a 1·5T machine, and MRA scans with 0·5T or 1·0T machines are not recommended.[68–71] Houkin and co-workers[72] have suggested a novel grading of MRA in moyamoya disease: MRA scores are assigned on the basis of the severity of the occlusive changes in the ICA, of the horizontal portions of the MCA, ACA, and posterior cerebral artery, and of the flow signals of the distal branches of these arteries. MRA scores correlated well with the six-stage classification on cerebral angiography, with a high sensitivity and specificity.[72]

MRI and MRA are non-invasive methods that can be repeated after surgery. T1-weighted MRI can be used to assess whether the moyamoya vessels in the basal ganglia and thalamus regress after surgery.[73] Serial MRA examinations have shown how neovascularisation occurs between the donor tissue and brain after surgery.[61] The results from a study by Houkin and co-workers[61] show that moyamoya vessels start to regress 1 month after combined bypass surgery, and that the deep temporal artery and the middle meningeal artery increase their calibres and can be identified 3 months after surgery. Stenotic change in the carotid terminations quickly progresses after surgery. Thus, there is a reciprocal relation between neovascularisation and the regression of moyamoya vessels (figure 4).[61]

SPECT, PET, and perfusion MRI

Data from several studies have shown specific patterns of cerebral haemodynamics and metabolism in patients with moyamoya disease: paediatric patients have lower cerebral blood flow (CBF) than age-matched controls, particularly after ischaemic stroke.[74,75] The distribution of CBF typically shows posterior dominance. Cerebrovascular reactivity to acetazolamide (figure 5) or carbon dioxide (ie, increase or decrease in carbon dioxide tension) is widely impaired in the territory of the ICA, which suggests reduced cerebral perfusion pressure (CPP).[74,76–79] This reduced CPP is compensated for by an increase in cerebral blood volume, oxygen extraction fraction, or both.[80,81] The disturbances in cerebral haemodynamics and metabolism are usually less prominent in adult patients with moyamoya disease than in paediatric patients.[79,81] Cerebral blood volume is diffusely increased in the territory of the ICA in most adult patients with moyamoya disease, which suggests that compensatory vasodilatation occurs in response to reduced CPP.[79,82–84] However, oxygen extraction fraction is within the expected limits in most adult patients,[82] although the haemodynamic and metabolic characteristics of moyamoya disease are not uniform, and severe haemodynamic compromise is seen in some patients.[85]

Cerebral haemodynamics and metabolism can change substantially after effective surgical revascularisation in

patients with moyamoya disease.[86] Thus, both CBF and the cerebrovascular reactivity of CBF to acetazolamide improve or normalise after surgery.[76,87] After surgery, the oxygen extraction fraction frequently normalises in patients who had a raised oxygen extraction fraction before surgery.[88–91] However, cerebral haemodynamics are often still impaired in the frontal lobes, even after surgery if the surgical field is confined to the temporoparietal area.[42,92] Single photon emission computed tomography (SPECT) or PET measurements might be useful to predict outcome in patients who have had surgical revascularisation.[93] Perfusion-weighted MRI is another technique that might be useful to assess cerebral haemodynamics in moyamoya disease. The mean transit time and cerebral blood volume might be key variables to identify reduced CPP.[94,95]

Surgical treatments

There are no effective medical therapies for moyamoya disease. Through the provision of collateral pathways, surgical revascularisation is the most successful therapy to improve cerebral haemodynamics, and to reduce the risk of subsequent stroke.[86] Surgical procedures for moyamoya disease can be classified into three categories: direct bypass, indirect bypass, and combined bypass. Direct bypass procedures include superficial temporal artery to MCA (STA–MCA) anastomosis.[96] The STA can also be anastomosed to the branch of the ACA in patients who have severe ischaemia in the ACA area.[97,98] The surgical procedure and technique are similar to those for patients with atherosclerotic, occlusive carotid artery diseases. Surgery can be technically challenging in some paediatric patients because their cortical branches have a smaller diameter and are more fragile than those of adults.[99,100] Direct bypass is useful to improve cerebral haemodynamics and to resolve ischaemic attacks immediately after surgery. The frequency of perioperative ischaemic stroke is lower after direct or combined bypass than it is after indirect bypass.[97] However, careful management of patients is needed after direct bypass surgery because postoperative pronounced changes in cerebral haemodynamics might induce hyperperfusion syndrome, particularly in patients with profound ischaemia before surgery.[101] Preoperative and postoperative SPECT studies and intraoperative blood flow measurements can be important to identify and prevent the serious complications caused by postoperative hyperperfusion.[102–104]

Surgical procedures for indirect bypass are specific for moyamoya disease. There are various methods for indirect bypass, including encephaloduroarteriosynangiosis,[105] encephalomyosynangiosis,[106] encephaloduroarteriomyosynangiosis,[107] encephalogaleosynangiosis,[108] and multiple burr hole surgery.[109] The STA, dura mater, temporal muscle, and galeal tissue have been used as the pediculate donor tissues in these techniques. Indirect bypass surgery that induces spontaneous angiogenesis between the brain surface and the vascularised donor tissues is technically simple to do and has been widely used.[110] However, the beneficial effects are not immediate because surgical

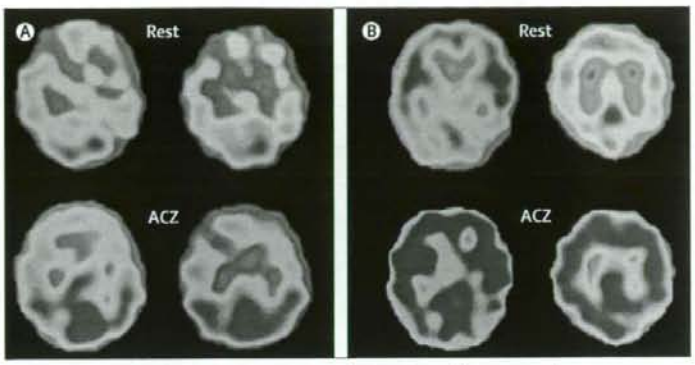

Figure 5: **Preoperative and postoperative SPECT in paediatric patients with moyamoya disease**
(A) Preoperative ^{133}xenon SPECT in a 6-year-old boy shows marked reduction of CBF and cerebrovascular reactivity to ACZ, particularly in the frontal lobes. (B) Postoperative ^{133}xenon SPECT shows normalisation of both CBF and cerebrovascular reactivity at 3 months after STA–MCA anastomosis and encephaloduromyoarteriopericranial synangiosis. ACZ=acetazolamide.

collaterals require 3–4 months to develop,[60,61,100] and there is a potential risk of perioperative ischaemic stroke.[111,112] Therefore, proper anaesthetic management is essential to prevent perioperative ischaemic complications.[113–115] Surgical design is also important because the extent of surgical collateral pathways depends on the size of the craniotomy and the extent of the indirect bypass.[98,116–118] Furthermore, collateral pathways through indirect bypass do not develop in about 40–50% of adult patients, although indirect bypass provides extensive surgical collaterals in almost all paediatric patients. Thus, direct bypass is particularly important for adult patients with moyamoya disease.[119,120]

Combined bypass procedures, which include both direct and indirect bypass, have the advantages of both procedures.[97,121] We have developed a novel procedure for combined bypass surgery to supply blood flow over a wide surface of the brain. In addition to the STA, dura mater, and temporal muscle, the pericranial flap can be used as donor tissue for indirect bypass through fronto-temporal craniotomy that covers large areas of the frontal lobe; this is known as encephaloduromyoarteriopericranial synangiosis. 58 patients have had single or double STA–MCA anastomosis and encephaloduromyoarteriopericranial synangiosis procedures in our hospital over 10 years. Postoperative cerebral angiography and SPECT or PET studies have shown that cerebral haemodynamics extensively improved in the operated hemispheres, including the frontal lobes. No more ischaemic or haemorrhagic strokes have been recorded after surgery, although longer follow-up is needed (Kuroda S and Houkin K, unpublished data).

Prognosis

Natural course

The natural history of moyamoya disease is not fully understood because there have been only a few studies on the progression of the disease. Early clinical investigations

have shown that functional or intellectual outcome were poor in paediatric patients who were treated conservatively (ie, no surgical treatment).[122,123] Kurokawa and co-workers[122] have shown that mild intellectual or motor impairment, or both, was seen in seven of 27 patients, and three patients needed to attend special school or receive care by parents or in an institution when they reached teenage years. Two of the patients needed 24-h care.[122] A longitudinal observational study has shown that the intelligent quotient scores of patients start to decrease 5 years after onset of moyamoya disease.[124] Infants are at higher risk for ischaemic stroke that is directly related to poor functional outcome.[125–127] Occlusive lesions in the carotid terminations commonly worsen in paediatric patients.[128]

The frequency of cerebrovascular events, including ischaemic and haemorrhagic strokes, is high in adults whose moyamoya disease is treated conservatively.[129–131] Hallemeier and co-workers[129] have shown that the 5-year risk of recurrent ipsilateral stroke was 65% in the medically treated symptomatic hemispheres of 34 adult patients with moyamoya disease. The 5-year risk increased up to 82% in adult patients with bilateral involvement and symptoms of ischaemia.[129] Recurrent haemorrhagic stroke (rebleeding) is still one of the most serious complications that worsens functional outcome and increases the mortality rate in adult patients with moyamoya disease.[132,133] During follow-up periods of 2–20 years, rebleeding occurred in about 30–65% of patients.[132–135] Rebleeding can occur at the original bleeding site at different sites.[93,120] A characteristic clinical feature of moyamoya disease is that a patient can have both ischaemic and haemorrhagic stroke; thus, ischaemic stroke can occur in patients with haemorrhagic stroke when their haemodynamic reserve is severely impaired.[136] Haemorrhagic stroke can also occur in a subgroup of patients with TIA or ischaemic stroke.[120]

Adult patients with moyamoya disease who have unilateral lesions should be carefully followed-up to monitor potential progression to bilateral lesions. The incidence of progression to bilateral disease might be higher than previously thought.[137–139] Smith and Scott[140] have shown that ten of 33 patients with unilateral moyamoya disease progressed to bilateral disease over 5 years. Contralateral abnormalities seen on initial imaging, congenital cardiac anomalies, previous cranial irradiation, Asian ethnic origin, and familial moyamoya syndrome were associated with an increased risk of disease progression.[140] Furthermore, the results from a cohort study[141] showed that disease progression occurred in 15 of 63 adult patients during the follow-up period of 73·6 months. Occlusive arterial lesions progressed in the anterior and posterior circulation territories, in both symptomatic and asymptomatic patients, and in both bilateral and unilateral disease. Eight of the 15 adult patients developed ischaemic or haemorrhagic events in relation to disease progression. Multivariate analysis showed that the odds ratio for disease progression for men with moyamoya disease was 0·20 (95% CI 0·04–0·97). Careful follow-up is thus important to prevent further stroke in adults with moyamoya disease who have been treated medically, even if these patients are asymptomatic or have been diagnosed with unilateral moyamoya disease.[141]

Outcome in asymptomatic adult patients

Since the development of non-invasive diagnostic methods such as MRI and MRA, the incidence of asymptomatic moyamoya disease has been shown to be higher than previously thought.[5,142,143] The natural course of asymptomatic moyamoya disease is not clear. A nationwide survey in Japan identified 40 asymptomatic patients (13 to 67 years of age).[5] At initial presentation, cerebral infarction and disturbed cerebral haemodynamics were detected in about 20% and 40% of the affected hemispheres, respectively. Correlation analysis showed that angiographic stage was more advanced in elderly patients than in younger patients. Of 34 patients who were not treated surgically,[5] three had TIA, three had intracranial bleeding, and one had ischaemic stroke during 43·7 months of follow-up. The annual risk for any stroke was 3·2%. The progression of disease was associated with ischaemic events or silent infarction in four of five patients. No cerebrovascular events occurred in six patients who underwent surgical revascularisation.[5] These findings suggest that asymptomatic moyamoya disease is not a silent disorder and might potentially cause ischaemic or haemorrhagic stroke.

Long-term prognosis after bypass surgery

There is a scarcity of randomised clinical trials to confirm the beneficial effects of surgical revascularisation on subsequent ischaemic stroke in moyamoya disease, probably because the number of patients with the disorder is small. On the basis of previous studies, however, surgical revascularisation is thought to improve cerebral haemodynamics and reduce the incidence of subsequent ischaemic stroke in both paediatric and adult patients. In paediatric patients, the incidence of TIA rapidly decreases or even disappears after surgery; furthermore, paediatric patients rarely develop further ischaemic stroke after surgery.[99,111,121,125,144–147] There are several predictors that help to determine long-term outcome, including the age of onset, procedure for surgical revascularisations, and postoperative cerebral haemodynamics.[93,127,148,149] Intellectual development is also impaired in a subgroup of paediatric patients.[18] Even after surgical revascularisation, intellectual impairment has been shown to disrupt an independent social life in more than 20% of paediatric patients whose ischaemic attacks had resolved after surgery.[111,124,144,150] Results from earlier studies have suggested that poor intellectual outcome correlates with early onset (<5 years), completed stroke, cerebral infarction, or a longer disease period.[150,151] Multivariate analyses have confirmed that completed stroke and small craniotomy surgery are independent predictors for poor intellectual outcome in paediatric patients who have had surgical revascularisation.[18] Small craniotomy surgery, such as encephaloduroarterio-

synangiosis and encephalomyosynangiosis, is technically easy but, as mentioned above, one of the disadvantages of this surgery is that the revascularised area is limited and is confined to the craniotomy field.[92] Therefore, early diagnosis and doing the revascularisation procedure over as wide an area as possible might be important to improve the intellectual outcome of the patients.

In adults with moyamoya disease, the risks of TIA and ischaemic stroke almost disappear in most patients when surgical revascularisation is done effectively. However, long-term follow-up is crucial to improve the prognosis because a few adult patients still have an ischaemic or haemorrhagic stroke, even after surgery.[89,129,130,152–154] Surgical revascularisation might reduce the incidence of rebleeding to 12·5–20% (from the estimated occurrence of 30–65%[132–135]), although the evidence levels of these studies are not high.[120,133,153,154] Direct or combined bypass surgery might reduce the risk of rebleeding and resolve the peripheral aneurysms in the collateral or moyamoya vessels.[91,155] The Japan Adult Moyamoya trial, a multicentre, randomised clinical study, is underway and will assess whether direct or combined bypass surgery can reduce the risk of rebleeding in adults with moyamoya disease.[156]

Conclusions and future perspectives

Although the incidence of moyamoya disease is not high, it is an important cause of cerebral stroke in children and adults. Prompt diagnosis and appropriate management are crucial to improve the long-term prognosis of patients. Further investigations are needed to clarify the aetiology of the disease and to develop clinical strategies to prevent ischaemic and haemorrhagic stroke. Genetic analysis of familial moyamoya disease might help to determine the pathogenesis of moyamoya disease in the near future. If the relevant genes could be identified, we might be able to develop novel gene therapies and prevent the occurrence of moyamoya disease in patients who are genetically susceptible. The ongoing Japan Adult Moyamoya clinical trial will also help to clarify the beneficial effects of direct or combined bypass surgery for the prevention of rebleeding. Further epidemiological and follow-up studies are needed to understand the natural course of asymptomatic moyamoya disease. These data will be important to refine the guidelines for medical and surgical treatments for moyamoya disease, particularly for patients who are asymptomatic or who have haemorrhagic stroke.

Search strategy and selection criteria

References for this Review were identified through searches of PubMed by use of the search term "moyamoya", from January, 1969 to June, 2008. Only papers in English or in Japanese with English abstracts were reviewed in detail. Further references were obtained from the bibliographies of the papers identified through our searches. The final reference list was generated on the basis of relevance to the topic of this Review.

Contributors

SK was involved in the planning and writing of the Review. KH was involved in the planning and revisions of the Review.

Conflicts of interest

We have no conflicts of interest.

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