

ため、モヤモヤ病におけるMBの真の潜在率、小児例における潜在率、症候性出血転化率、それらに抗血小板治療や高血圧、血行再建術が与える影響について正確な情報を得るには大規模前向き研究が必要である。

モヤモヤ病研究班では多施設間共同研究として大規模MRIデータベースを用いた研究を計画し2005年度には165症例が登録された。今後前向き研究によりMBがモヤモヤ病の出血に果たす役割が明らかになることが期待される。

E 結論

モヤモヤ病患者においてはMRI T2*強調画像により無症候性脳内微小出血巣(MB)が健常者に比べ有意に高頻度に検出される。モヤモヤ病の出血発症におけるMBの意義を検証するため、今後大規模前向き研究が必要である。

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症例	1	2	3	4	5	6	7	8	9	10	11
年齢(歳)	41	65	27	36	49	24	63	28	44	35	53
性	女	男	女	女	男	女	女	女	女	女	女
発症様式	虚血型	虚血型	虚血型	虚血型	虚血型	虚血型 術後遅発性 出血	虚血型 術後遅発性 出血	虚血型 術後遅発性 出血	出血型	出血型	出血型
臨床経過	2001年12月脳梗塞	1945年TIA	2003年11月TIA	1999年10月TIA	2003年11月脳梗塞	1987年TIA 2003年10月脳出血	1981年脳梗塞 1985脳出血 1987年脳出血 1999年脳出血	1981年TIA 1998年脳出血	2000年8月脳出血	1999年11月脳出血	1979年11月脳出血
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3テスラMRI検査日	術後 2003年11月	術前 2003年11月	術前 2003年12月	術後 2004年3月	術前 2004年4月	術後 2003年10月	術後 2004年3月	術後 2004年2月	術前 2003年11月	術後 2004年3月	術後 2004年3月
MRI所見(T2*画像)											

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Novel Magnetic Resonance Angiography Stage Grading for Moyamoya Disease

Kiyohiro Houkin^a Naoki Nakayama^c Satoshi Kuroda^c Tadashi Nonaka^a
Takaharu Shonai^b Takashi Yoshimoto^d

Departments of ^aNeurosurgery and ^bRadiology, Sapporo Medical University;
^cDepartment of Neurosurgery, Hokkaido University Graduate School of Medicine, Sapporo;
^dDepartment of Neurosurgery, Tohoku University, Sendai, Japan

Key Words

Moyamoya disease · Magnetic resonance angiography · Staging · Angiography

Abstract

Background: Magnetic resonance angiography (MRA) has been acknowledged as a noninvasive diagnostic modality for moyamoya disease. However, in terms of staging of moyamoya disease, conventional angiography is still the gold standard. Therefore, the purpose of this study was to establish MRA grades for moyamoya disease as an alternative to conventional angiography. **Methods:** Twenty-two patients (44 sides) with moyamoya disease diagnosed by conventional angiography were evaluated by MRA during the past 5 years. MRA scores were assigned based on the severity of occlusive changes of the internal carotid artery, the horizontal portion of the middle cerebral artery, the anterior and the posterior cerebral arteries and the signals of the distal branches of these arteries. Total points ranged from 0 (normal) to 10 (most severe). **Results:** MRA scores (0–10) were significantly consistent with the conventional angiographic staging. Four grades based on this novel MRA scores correlated well with Suzuki's stages, with high sensitivity and specificity. **Conclusions:** These novel MRA grades

can be a reliable alternative to conventional staging. By employing these novel MRA grades, the use of conventional angiography can be avoided for the purpose of evaluation of the stages of moyamoya disease.

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Introduction

Magnetic resonance angiography (MRA) has been widely used as a noninvasive diagnostic modality following its official introduction into the guidelines for the diagnosis of moyamoya disease in Japan by the Japanese Ministry of Health and Welfare in 1997 [1–3]. Since then, MRA has been acknowledged as a reliable diagnostic tool with high sensitivity and specificity as a result of the remarkable development of MR imaging technology [4–11].

However, it is well known that moyamoya disease is a dynamically changing disease and these changes are observed angiographically, ranging from a very early stage of equivocal mild stenotic change in the intracranial artery without moyamoya vessels to an end stage with the occlusion of the carotid fork and remarkable development of collateral circulation [12–14]. Dynamic changes that drastically modify the angiographic findings include

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Kiyohiro Houkin, MD, DMSc
Department of Neurosurgery
Sapporo Medical University
S-1, W-16, Sapporo 060-8543 (Japan)
Tel. +81 11 611 2111, Fax +81 11 614 1662, E-Mail houkin@sapmed.ac.jp

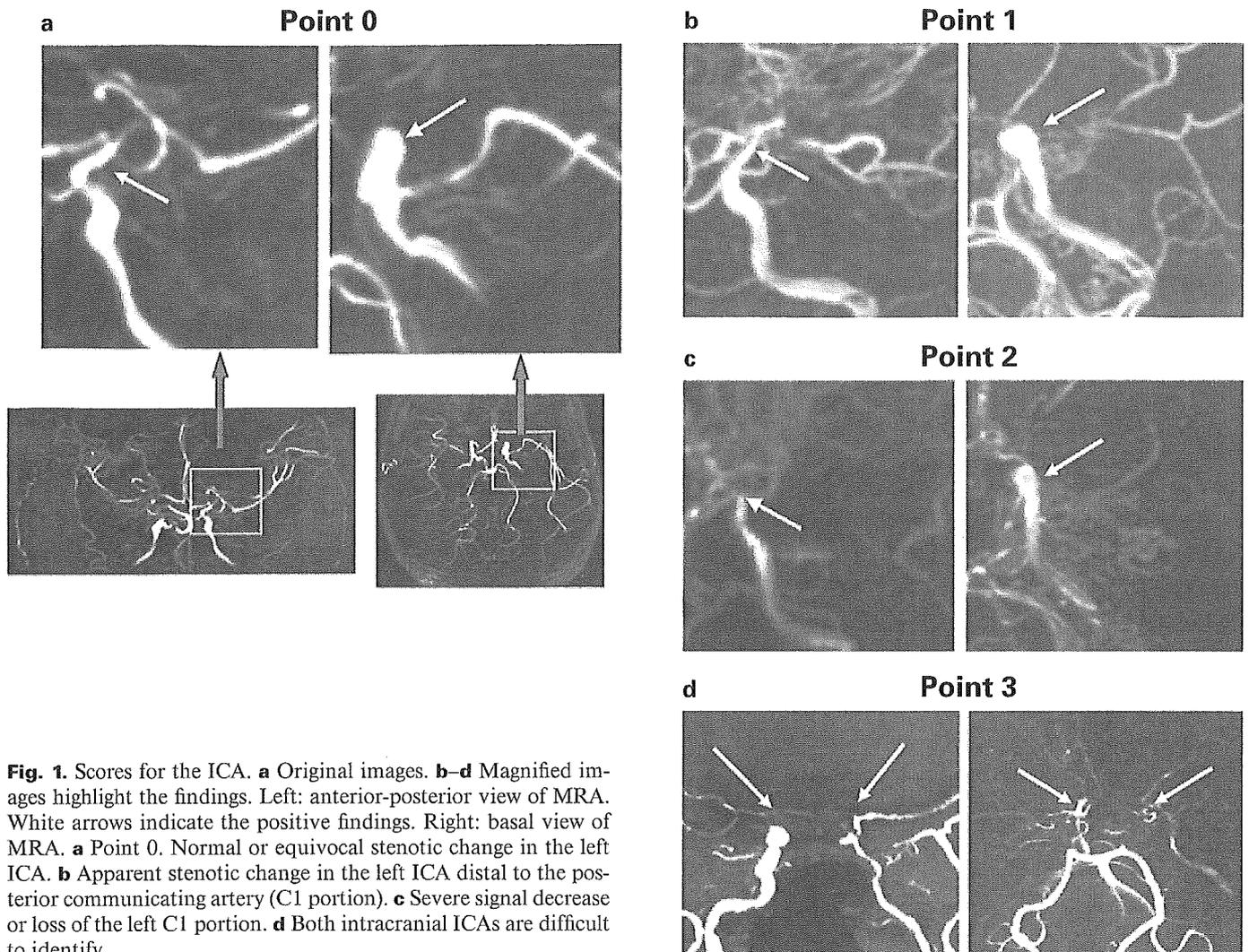


Fig. 1. Scores for the ICA. **a** Original images. **b–d** Magnified images highlight the findings. Left: anterior-posterior view of MRA. White arrows indicate the positive findings. Right: basal view of MRA. **a** Point 0. Normal or equivocal stenotic change in the left ICA. **b** Apparent stenotic change in the left ICA distal to the posterior communicating artery (C1 portion). **c** Severe signal decrease or loss of the left C1 portion. **d** Both intracranial ICAs are difficult to identify.

development of moyamoya vessels and collateral anastomosis, which follows the initial steno-occlusive change of the carotid fork [12]. Suzuki's staging is well recognized as the standard angiographic staging based on these particular changes observed in moyamoya disease [13]. Therefore, as far as its staging is concerned, conventional angiography is still the gold standard. However, as it is well known, the catheter angiography has general risks of complication, including rare serious complication such as mortality. In addition, it often requires anesthesia for pediatric moyamoya patients, which is not always safe.

In this study, we investigated the possibility of evaluating the stage of moyamoya disease using a contemporary MR machine. Novel MRA scoring and grades are proposed as an alternative to conventional angiography.

Patients and Methods

Subjects

Twenty-two patients (44 sides) were preoperatively examined by both conventional angiography and MRA for a period of 5 years between January 1997 and December 2001. The mean age of the patients was 19.0 ± 19.5 years (range 1–68 years), and included 15 pediatric patients under the age of 15 years and 7 adults above the age of 15 years.

Magnetic Resonance Angiography

MRA was obtained using the three-dimensional time of flight technique with three-dimensional spoiled gradient recalled echo sequence using 1.5-tesla magnet machines. The imaging parameters were as follows: flip angle = 20° , time of repetition = 37 ms, echo time = 6.9 ms, band width = 15.63 kHz, field of view = 160×160 mm, scan thickness = 0.8 mm, locations per slab = 48 (8 overlaps), 2 slabs, matrix = 512×256 , acquisition = 1, and imaging time = 8 min 30 s.

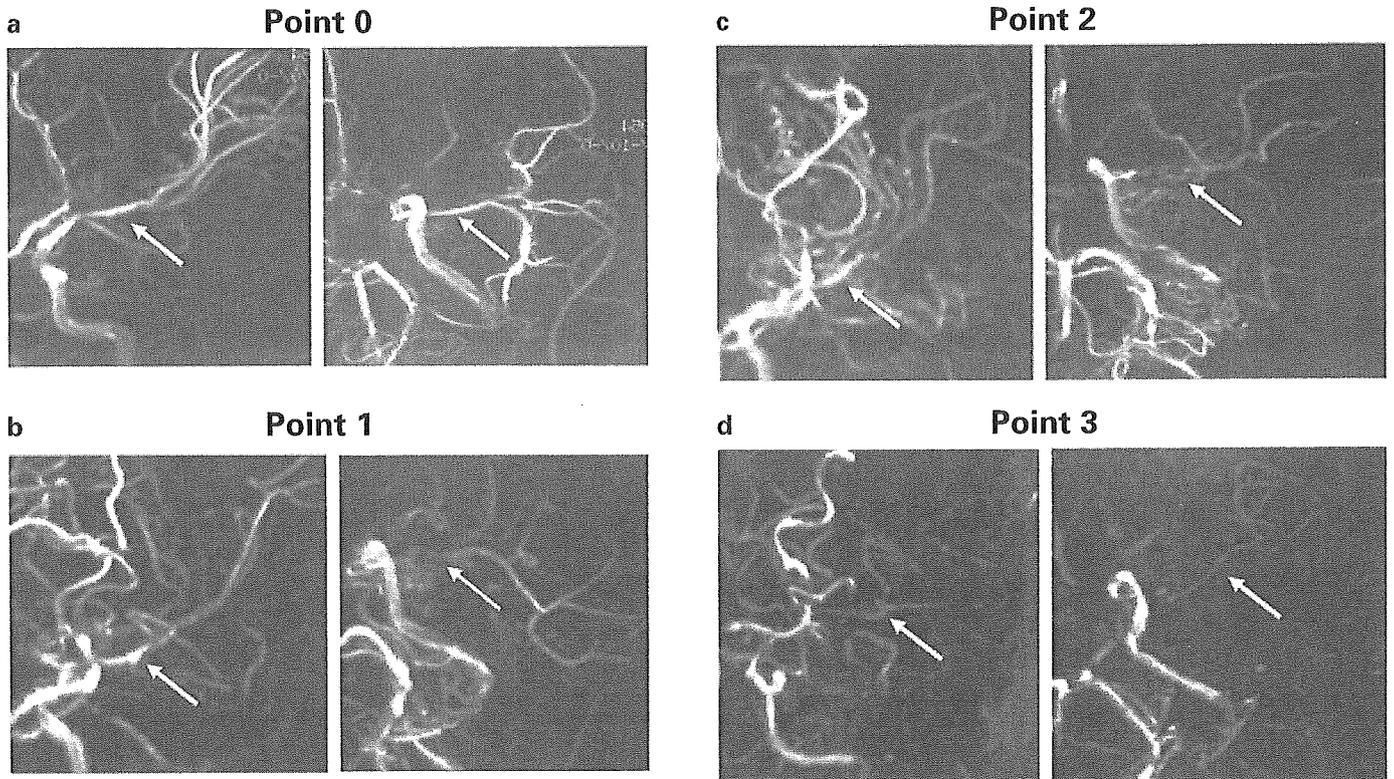


Fig. 2. Scores for the MCA. **a** Normal or equivocal stenotic change in the left M1 portion. **b** Moderate stenotic change in the horizontal portion of the left MCA (M1). **c** Severe signal decrease or loss of the left M1 portion and its distal branches. **d** The left M1 portion and its distal branches are difficult to identify.

MRA Score

Depending on the severity of its steno-occlusive change, a point was assigned to each of the internal carotid artery (ICA), the middle cerebral artery (MCA), the anterior cerebral artery (ACA) and the posterior cerebral artery (PCA) (table 1). It is well recognized that in moyamoya disease the anterior circulation (ICA, MCA, ACA) is mainly involved. However, recent studies frequently refer to similar steno-occlusive changes in the PCA [12–14]. All intracranial arteries, including PCA, are clearly depicted by MRA. Therefore, in this study, PCA was also evaluated.

Internal Carotid Artery. The intracranial portion of the ICA (fig. 1) was evaluated. The extracranial portion, including the cavernous portion was excluded from this evaluation because it does not show specific findings in moyamoya disease. Scores are assigned to the ICA depending on the severity of the steno-occlusive change of the horizontal portion of the MCA (M1) and the visibility of its distal branches. Point 0: normal or minimum equivocal change of the ICA; point 1: apparent stenosis at the intracranial carotid artery (C1 portion, distal to the posterior communicating artery); point 2: discontinuity of the signal of the C1 portion. point 3: no depiction of the intracranial ICA.

Middle Cerebral Artery. Scores were assigned to the MCA (fig. 2) depending on the severity of the steno-occlusive change of the horizontal portion of the MCA (M1) and the visibility of its distal

Table 1. Summary of the MRA score

ICA		
Normal		0
Stenosis of C1		1
Discontinuity of C1 signal		2
Invisible		3
MCA		
Normal		0
Stenosis of M1		1
Discontinuity of M1 signal		2
Invisible		3
ACA		
Normal A2 and its distal		0
A2 and its distal signal decrease or loss		1
Invisible		2
PCA		
Normal P2 and its distal		0
P2 and its distal signal decrease or loss		1
Invisible		2
Total		0~10

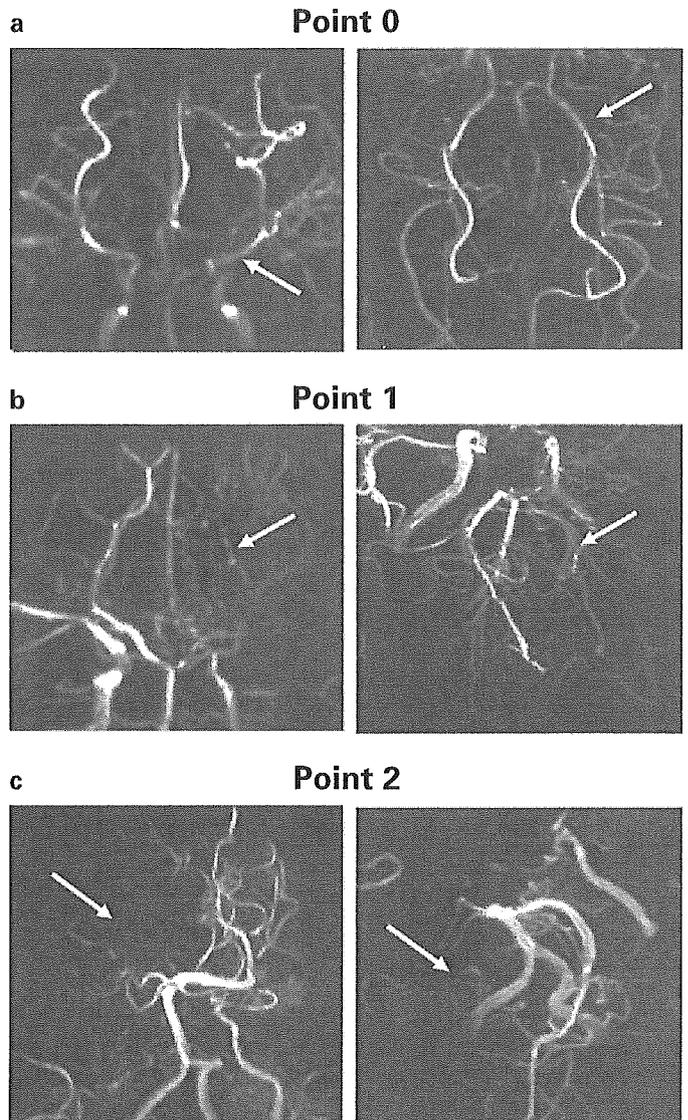
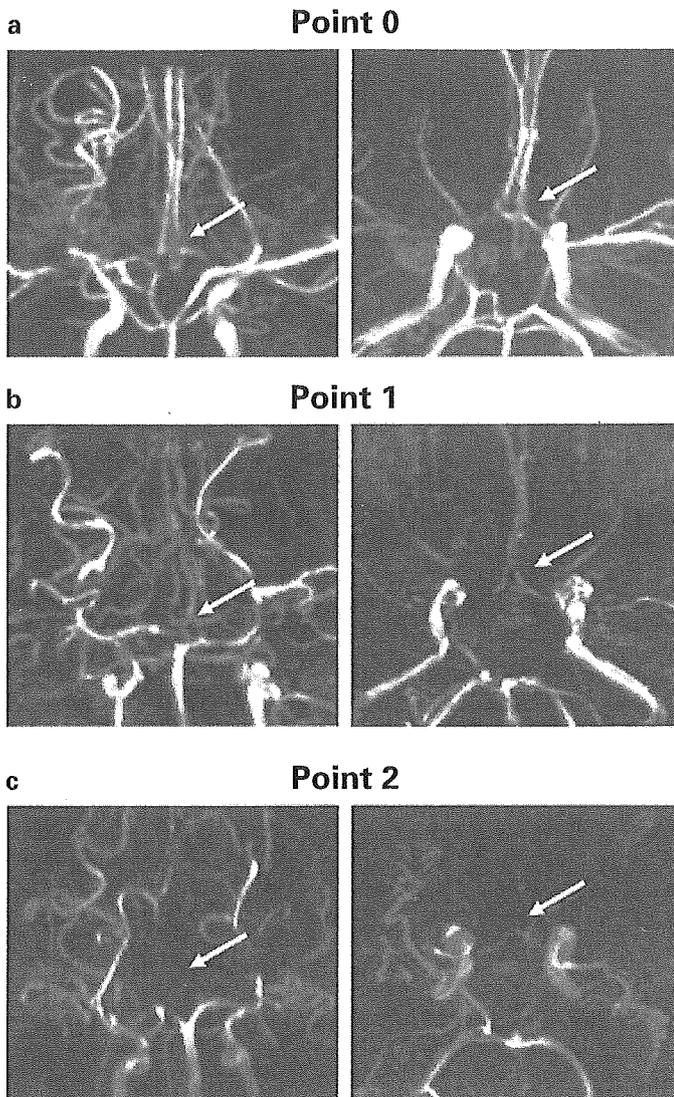


Fig. 3. Scores for the ACA. **a** Normal or equivocal stenotic change in the distal ACA (A2 portion). **b** Signals of both A2 and its distal branches decrease. **c** Both distal ACAs are difficult to identify.

Fig. 4. Scores for the PCA. **a** Normal or equivocal stenotic change in the ambient segment of the PCA (P2 portion). **b** Signals of the left P2 and its distal branches decrease. **c** The right P2 is difficult to identify.

branches. Point 0: normal or minimum equivocal change of the horizontal portion of the MCA (M1 portion), including its wall irregularity; point 1: stenosis of the horizontal portion of the MCA with normal or equivocal signal diminishment of its distal branches; point 2: discontinuity of signal of the horizontal portion of the MCA and decrease of the signal of distal MCA; point 3: no depiction of most of the MCA territory.

Anterior Cerebral Artery. It is well known that the horizontal portion of the ACA (A1) is often hypoplastic on the basis of its reciprocal relation to the other side of A1. Therefore, the ACA (fig. 3) was evaluated based on the visibility of the A2 portion and its distal branches. Point 0: normal signal intensity of the A2 and its dis-

tal branches; point 1: signal decrease or loss of the A2 and its distal branches; point 2: no depiction of the ACA.

Posterior Cerebral Artery. Scores were assigned to the PCA (fig. 4) depending on the visibility of the ambient segment (P2) and its distal branches because the first segment of the PCA is occasionally hypoplastic as a normal variation. Point 0: normal or equivocal stenotic change of the P2 and its distal branches; point 1: signal decrease or loss of P2 and its distal branches diminishes; point 2: no depiction of the PCA.

The moyamoya vessels were excluded from the evaluation of subjects because the depiction of these small vessels is not always constant. In addition, it is well known that their development is not

Table 2. Correlation between MRA scores and MRA grades

MRA score	MRA grade
0-1	1
2-4	2
5-7	3
8-10	4

related to the severity of this disease. Once they are formed, the moyamoya vessels regress as the disease progresses [12-14]. Radiological scoring, including our novel MRA grading, therefore, does not reflect the clinical severity of moyamoya disease.

The MRA score was defined as the total points of the four main cerebral arteries. The minimum score is 0 and the highest score is 10 (ICA3 + MCA3 + ACA2 + PCA2 = 10). It is expected that with the progress in the stage of the disease, the score should also increase.

The MRA score was independently evaluated on each side of every subject by independent observers (N.N., K.H., T.N.) without knowledge of the data obtained by conventional angiography. Next, it was compared with Suzuki's angiographic stages.

Novel MRA Stage Grading

The most important goal of this study was to establish a more convenient system of grading moyamoya disease using MRA. We intended to establish an MRA grading system, which is simpler and more convenient than Suzuki's staging. Indeed, for this purpose, we have tried many grading systems as a background study. As described in Results, the novel grading system (table 2) revealed the best correlation with conventional Suzuki's staging, as shown by the p values and kappa statistics.

The MRA score was classified into four grades for more convenient evaluation of the progress of the disease (table 2). In a clinical scenario, Suzuki's stages I and II are considered as the early stages of moyamoya disease. Stages III and IV, which are the most frequently observed stages, are clinically important and have to be clinically discriminated. Suzuki's stages V and VI are considered the final stages of moyamoya disease.

Statistical Analysis

Interobserver Difference. In this study, 3 observers independently evaluated MRA score for 44 sides of 22 patients. In order to confirm the agreement between the observers, Kendall's coefficient of concordance was calculated based on kappa statistics.

Correlation between MRA Scoring and Conventional Suzuki's Angiographic Stages. MRA scoring and Suzuki's stages are non-parametric values. Therefore, χ^2 test was used to confirm the correlation between these two scores. In addition, Cramer's V coefficient was calculated to show the correlation between these two non-parametric scores. It is known that the strong correlation is estimated when this Cramer's V coefficient is larger than 0.7.

Correlation between MRA Grading and Suzuki's Stages. χ^2 test was used. Kappa statistics was also calculated.

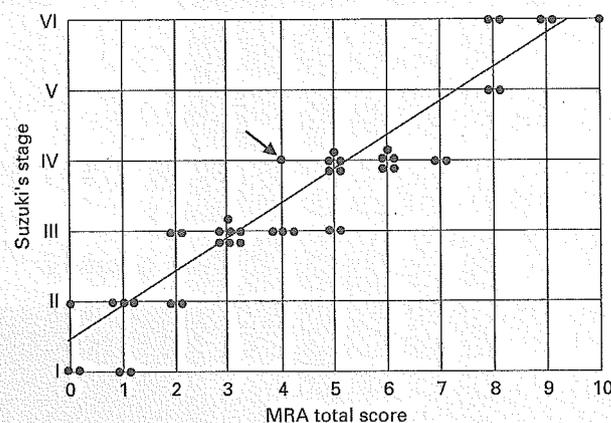


Fig. 5. Correlation between total MRA scores and conventional angiographic stages. Each point represents one side of MRA. The arrow indicates one side of a patient that shows total MRA score of 4 and Suzuki's stage IV. Total number of sides is 44.

Results

Inter-Observer Difference

The correlation between the scores evaluated by 3 independent observers was evaluated. The p value was <0.001 and Kendall's coefficient of concordance was 0.99. This suggests that there was a statistically significant concordance between the observers.

Correlation between MRA Scoring and Conventional Suzuki's Angiographic Stages

Figure 5 shows the correlation between the MRA scores and Suzuki's angiographic stages in 22 patients (44 sides). As the angiographic stage progresses, the MRA score also increases. Thus, a good correlation was revealed between the conventional angiographic stage and this MRA score since χ^2 test calculated that p value was smaller than 0.0001 and Cramer's V coefficient was 0.77. A demonstrative case is shown in figure 6.

Correlation between MRA Grading and Suzuki's Stages

As a result, this novel MRA grading correlated well with conventional staging (table 3). In the statistical analysis, this 4 × 6 table was analyzed by χ^2 test. p value was 0.001 (8.68×10^{-10}) and kappa statistics was 0.84452, which suggested that the correlation between these two grading systems is quite good.

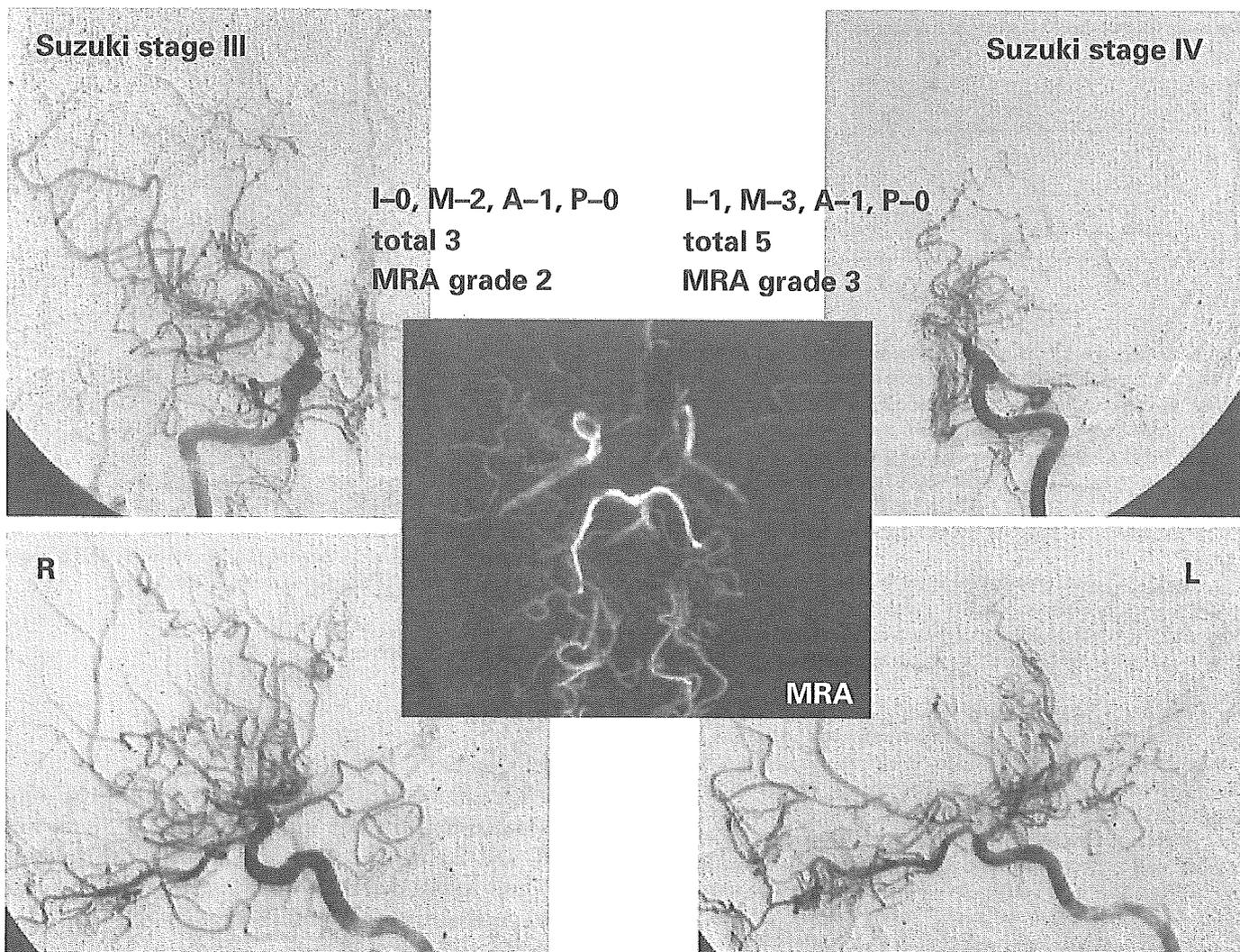


Fig. 6. Demonstrative case of the correlation between the MRA grade and the angiographic stage. In this case, conventional angiographic stage is III for the right side and IV for the left side. MRA grades are 2 for the right side and 3 for the left side.

Discussion

It was clearly shown by Suzuki and Takaku [15] and Suzuki and Kodama [16, 17] that moyamoya disease is a progressive disease. Angiographic findings reveal that this disease shows rather dynamic changes that reflect the reciprocal relation between the progressive steno-occlusive change of the carotid fork and the development of collateral circulation. It is well known that there are two types of collateral networks, namely, moyamoya vessels that develop mainly at the basal ganglia and transdural anastomosis [15]. Based on these principles and important facts, Suzuki and Takaku [15] and Suzuki and Ko-

dama [16, 17] classified this disease into 6 stages considering two factors: the severity of the steno-occlusive change and the development of collateral circulation. Their classification is, therefore, based on these two factors. To date, conventional angiography was indispensable for establishing the stage of moyamoya disease based on their classification [1, 2].

Meanwhile, we have already reported that MRA is a reliable alternative to conventional angiography in terms of diagnosis of moyamoya disease [1-3]. In brief, if the steno-occlusive change and development of moyamoya vessels are recognized by MRA and MRI, the diagnosis of moyamoya disease is definite even without performing

Table 3. Correlation between MRA grades and Suzuki's angiographic stages

MRA grade	Suzuki's stage					
	I	II	III	IV	V	VI
Grade 1 (MRA score 0-1)	4	4				
Grade 2 (MRA score 2-4)		2	12	1		
Grade 3 (MRA score 5-7)			2	12		
Grade 4 (MRA score 8-10)					2	5

Each number represents the number of sides. Total number of sides is 44.

conventional angiography. Indeed, a study of many published papers on moyamoya disease reveals that MRA plays an important role in reaching a definite diagnosis these days [3-19]. In addition, we have also reported that postoperative dynamic angiographic changes that include both direct bypass and angiogenesis induced by an indirect bypass are revealed by MRA [20, 21].

After the introduction of MRA as a diagnostic tool, the possibility of its use in the staging of moyamoya disease has been expected as a logical consequence. If we establish the novel MRA scoring system for the staging of moyamoya disease, both the limitations and advantages of this particular modality and the features of moyamoya disease described above have to be carefully considered. As expected, the most controversial point in terms of MRA scoring is whether the development of moyamoya vessels should be considered.

The detection of well-developed basal moyamoya vessels is not always difficult using the contemporary high-tesla MR machine. Therefore, it is quite practical to evaluate the development of basal moyamoya vessels and include this factor into the scoring system. However, it is well known that the development of basal moyamoya vessels is not linearly correlated with the staging of this disease [3, 16]. In its early stage, there is insufficient development of basal moyamoya vessels, and similarly, in its end stage, basal moyamoya vessels vanish due to the development of transdural collateral circulation such as the vault moyamoya vessels [15-17]. Therefore, the scoring based on the development of moyamoya vessels is not always a good parameter for evaluating its stage. The eval-

uation of moyamoya vessels is indispensable for the primary diagnosis of this disease using MRA. However, once it is diagnosed, the evaluation of its steno-occlusive change is more practical for the staging of the disease.

In this paper, we reveal that this novel MRA scoring method, which is mainly based on the relative signal deterioration of the main branches of the cerebral artery reflecting the steno-occlusive changes in the circle of Willis, is a suitable alternative to conventional Suzuki's staging based on conventional angiography. It is true that careful observation of the signal intensity of main branches by an imaging condition is required to apply this MRA score because overestimation of the stenosis and occlusion are occasionally observed on MRA, as reported in numerous papers. In this MRA scoring method, this overestimation is also considered.

Suzuki's angiographic staging does not necessarily relate to the clinical severity and cerebral blood flow. This point is also considered in this MRA scoring method. The MRA of the time of flight method does not clearly reflect the collateral pathway formed at the periphery [3, 4]. Theoretically, MRA using a phase contrast method that reflects slow flow has the possibility to reflect cerebral circulation. However, the poor spatial resolution and long data acquisition time of the phase contrast technique is a practical limitation for considering MRA scoring as a standard method for evaluation of the stages of moyamoya disease.

Conclusion

A novel MRA scoring system was designed that is based on the steno-occlusive change of the carotid fork, the origin of the MCA, the anterior and posterior cerebral arteries and loss of signals of the distal branches of four main trunks. This MRA scoring correlated significantly with the conventional angiographic staging, and it can be a reliable alternative to conventional angiography for the purpose of staging of moyamoya disease and for the follow-up of vascularization changes. This is a great boon for patients with moyamoya disease, particularly for pediatric patients.

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