Table 3 Clinical data of the 59 cases in Group I-A

Mean age at delivery, yrs	29.2 ± 4.1
Mean weeks of gestation at delivery	36.9 ± 3.6
Previous deliveries	
none	32 (54.2%)
one	21 (35.6%)
two	4 (6.8%)
three	2 (3.4%)
Previous bypass surgery	
yes	34 (57.6%)
no	24 (40.7%)
unknown	1 (1.7%)
Cerebral events during gestation	
yes	3 (5.1%)
ICH	1
TIA	2
no	56 (94.9%)
Delivery method	
vaginal delivery	14 (23.7%)
natural labor	3
painless labor	11
caesarean section	45 (76.3%)
scheduled	41
emergent	2
others	2
Cerebral events during delivery and puerperium	
yes	0 (0.0%)
no	55 (100%)
ADL at discharge	
unchanged	58 (98.3%)
deteriorated	1 (1.7%)
Prognosis of the child	
alive, no sequela	54 (91.5%)
alive, status unknown	2 (3.4%)
deceased through abortion	2 (3.4%)
deceased (SIDS)	1 (1.7%)

ADL: activities of daily living, ICH: intracerebral hemorrhage, SIDS: sudden infant death syndrome, TIA: transient ischemic attack.

undergone previous bypass surgery, no statistical significance was found ($p = 0.07$).

Three cerebral events (5.1%) occurred during gestation (intracerebral hemorrhage in 1 case and transient ischemia in 2). A 30-year-old primipara who had been treated with EC-IC bypass developed intracerebral hemorrhage requiring emergent brain surgery. Although the child was delivered successfully by scheduled caesarean section at 32 weeks of gestation, this patient remained severely disabled (mRS 4). No sequelae were noted in the other two cases. No attacks occurred during delivery or during the puerperal period, and the neonates exhibited no problems associated with their mothers' MMD. Two stillbirths were delivered by intentional abortion, and one death during the infantile period was diagnosed as sudden infant death syndrome unrelated to MMD.

II. Group I-B (cases of MMD newly diagnosed)

Perinatal cerebrovascular attacks occurred in 5 patients with undiagnosed MMD. Figure 1 shows the demographics and clinical course of these patients. The mean age at delivery was 30.0 ± 4.9 years. Three patients presented with intracranial hemorrhage, and 2 suffered cerebral ischemia. Case 1 had previously delivered twice developed intracranial hemorrhage during pregnancy and was newly diagnosed with MMD. After emergent brain surgery, her gestation continued and she delivered a baby by scheduled caesarean section at 37 weeks. The maternal outcome was good (mRS 0) and the child survived (although no reply was received regarding any deficits in the child). Case 2 was a primipara who experienced serious intracerebral hemorrhage during pregnancy (no data was provided regarding weeks of gestation). Although an emergency craniotomy and caesarean section were performed, the mother eventually died; the child exhibited no deficit. Case 3 primipara developed intracranial hemorrhage during natural vaginal labor at 39 weeks of gestation. The child was delivered by emergent caesarean section without deficits, but the mother was rendered disabled (mRS 2). Case 4 suffered an ischemic attack during pregnancy and MMD was diagnosed. An elective caesarean section was performed at 37 weeks of gestation and no deficit remained in either mother or child. Case 5 developed severe pregnancy-induced hypertension accompanied by fetal distress syndrome, which required a caesarean section at 31 weeks of gestation. The delivery was uneventful, but the patient developed a cerebral infarction 3 days after delivery, resulting in mild neurological deficits (mRS 1). The infant also exhibited a sequela caused by the fetal distress.

Results of Survey II

Feedback was obtained from 338 female patients (for a response rate of 61.0%). Among these, 146 patients (43.2%) had undergone 278 deliveries. Forty-seven patients had already been diagnosed with MMD before their first pregnancy, whereas 97 patients were diagnosed after delivering all their children. Another two patients were diagnosed with MMD after their first or second deliveries and subsequently gave birth to other infants. Thus, all deliveries could be divided into two groups: 76 deliveries by 49 patients with previously diagnosed MMD (Group II-A), and 202 deliveries by 99 patients unaware of their MMD at childbirth and diagnosed later in life (Group II-B).

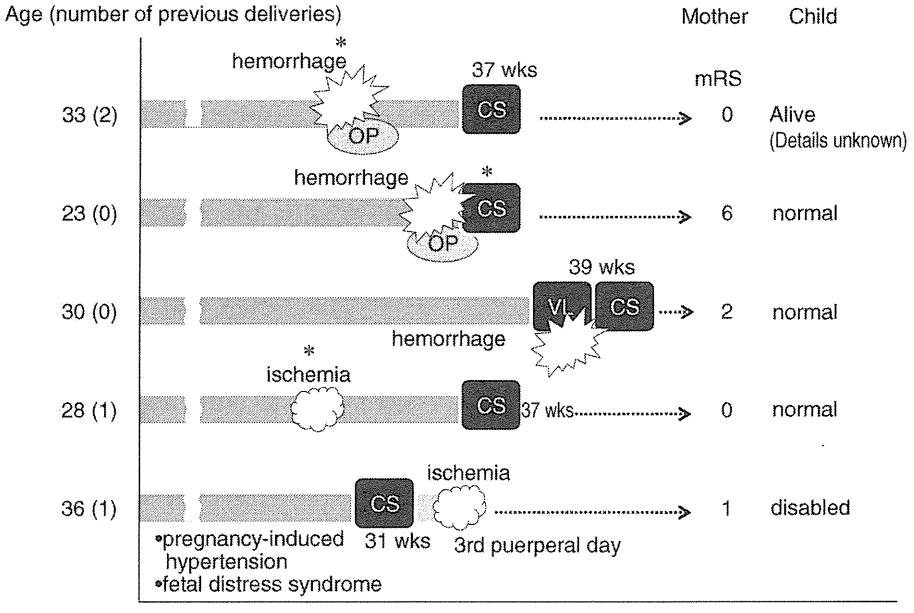

Fig. 1 Clinical course of the five cases in Group I-B. CS: caesarean section, mRS: modified Rankin scale, OP: neurosurgical operation, VL: vaginal labor. *Weeks of gestation unknown.

I. Group II-A (cases of MMD diagnosed previously)

Table 4 shows the clinical data. The mean age of diagnosis with MMD was 13.2 ± 8.2 years (1 to 34 years), and 71.4% of the patients were diagnosed before the age of 20 years. EC-IC bypass was performed in 44 (89.8%) patients and 63 (82.9%) deliveries occurred after surgical treatment. Among all 76 deliveries, 23 (30.3%) were vaginal deliveries, and 53 (69.7%) underwent caesarean section. The occurrence of previous bypass surgery had no significant effect on the selection of delivery methods ($p = 0.37$).

Neurological events were detected in 5 (6.6%) deliveries. Although all these patients had undergone bypass surgery previously, the incidence of the event in surgically-operated cases was not significantly different from non-operated cases ($p = 0.38$). Two events occurred during delivery and three occurred during the puerperal periods, and all were transient, leaving no deficit. The incidence of neurological events did not differ between vaginal delivery and caesarean section ($p = 0.51$). No neurological events were reported during these pregnancies.

II. Group II-B (cases of MMD undiagnosed at childbirth)

Table 5 shows detailed data. The mean age at diagnosis of MMD was 43.1 ± 10.7 years (23 to 69 years), and it is difficult to clarify whether the patients in this group had already contracted MMD or the level of severity. Among all 202 deliveries, 183 (90.6%) were vaginal deliveries, while caesarean section was employed in 19 (9.4%) cases. Transient neurological events were noted in four (2.0%) cases, all related to vaginal delivery. No serious events occurred leading to deficits, and no adverse events during pregnancy were reported.

Discussion

This is the first nationwide survey of pregnancy and delivery associated with MMD in Japan. The authors designed a survey for all the perinatal medical centers intended to reveal the current clinical situation regarding pregnancy and delivery associated with MMD (Survey I). While this design has the advantage of providing accurate medical information on each delivery, it also has the potential disadvantages of limiting each observation period to only a single perinatal period while failing to extract information about the medical history of each patient. This information is important, especially when a patient has given birth repeatedly. Another survey, therefore, was designed as Survey II. A major limitation must be noted, that patients who responded to the questionnaire were likely to be those in relatively good condition, as any fatalities or severely-disabled patients would have dropped out (inclusion bias). Furthermore, there might be some recall bias in this type of survey. Accordingly, the results must be

Table 4 Clinical data of the 76 deliveries in Group II-A (49 patients)

Mean age at present (range), yrs	34.6±6.6 (20 to 49)
Mean age upon diagnosis of MMD (range), yrs	13.2±8.2 (1 to 34)
Clinical type of MMD	
ischemic	31 (63.3%)
hemorrhagic	7 (14.3%)
ischemic to hemorrhagic transformation	2 (4.1%)
others or unknown	9 (18.4%)
Number of deliveries by each patient	
one	27 (55.1%)
two	17 (34.7%)
three	5 (10.2%)
Previous bypass surgery	
yes	63 (82.9%)
no	10 (13.2%)
unknown	3 (3.9%)
Delivery method	
vaginal delivery	23 (30.3%)
natural labor	21
painless labor	2
caesarean section	53 (69.7%)
scheduled	47
emergent	4
others	2
Neurological events during delivery and puerperium	
yes	5 (6.6%)
vaginal delivery	
TIA during delivery	1
TIA during puerperium	1
caesarean section	
seizure during delivery	1
unknown during delivery	1
TIA during puerperium	1
no	67 (88.1%)
unknown	4 (5.3%)

MMD: moyamoya disease, TIA: transient ischemic attack.

Table 5 Clinical data on the 202 deliveries in Group II-B (99 patients)

Mean age at present (range), yrs	50.8±10.9 (28 to 73)
Mean age upon diagnosis of MMD (range), yrs	43.1±10.7 (23 to 69)
Clinical type of MMD	
ischemic	32 (32.3%)
hemorrhagic	26 (26.3%)
ischemic to hemorrhagic transformation	5 (5.1%)
others or unknown	36 (36.4%)
Number of deliveries by each patient	
one	23 (23.2%)
two	54 (54.5%)
three	18 (18.2%)
more	4 (4.0%)
Delivery method	
vaginal delivery	183 (90.6%)
natural labor	182
painless labor	1
caesarean section	19 (9.4%)
scheduled	9
emergent	10
Cerebral events during delivery and puerperium	
yes	4 (2.0%)
vaginal delivery	
syncope during delivery	1
syncope during puerperium	1
TIA during puerperium	2
no	188 (93.1%)
unknown	10 (5.0%)
Bypass surgery after childbirth	
yes	58 (58.6%)
no	37 (37.4%)
unknown	4 (4.0%)

MMD: moyamoya disease, TIA: transient ischemic attack.

viewed with careful consideration for these biases.

This survey revealed that the incidence of the serious perinatal neurological complications is low when MMD has been diagnosed and treated previously. The one case of intracerebral hemorrhage during the gestational period, however, indicates that this group still has a risk of devastating perinatal stroke. In general, pregnancy induces various physiological changes including hypercoagulability, pregnancy-induced hypertension, and eclampsia.[4,14] Accordingly, intracranial ischemic and hemorrhagic attacks are believed to increase in pregnancy.[5,17]

In MMD, an EC-IC bypass has been reported to apparently improve hemodynamic ischemia,[10,11] so it is possible that previous surgical treatments serve to protect against perinatal ischemic stroke to some extent. However, neither positive nor negative effect of EC-IC bypass on the pregnancy and delivery with MMD was proved in this survey. As for intracranial hemorrhage, the preventive effect of an EC-IC bypass remains totally unproven[3,18] and is now under examination in the Japan Adult Moyamoya Trial, which is a randomized controlled trial to study the effect of EC-IC bypass surgery on hemorrhagic MMD.[9]

Scheduled caesarean section was employed in over two-thirds of the patients already diagnosed with MMD, and no serious events were noted during delivery. This selection could be the result of an obstetrician's decision to avoid hyperventilation and excessive elevation of blood pressure during natural labor. However, the present study detected no serious stroke during vaginal delivery. Therefore, there seems to be no evidence that vaginal delivery should be avoided in cases of MMD. It is notable that painless labor with epidural anesthesia was successfully undertaken in many of the recent cases of vaginal delivery with MMD in Survey I.

At present, there is no definite evidence for the

management of pregnancy with already diagnosed MMD. However, in terms of the perinatal physiological changes and the susceptibility to both ischemic and hemorrhagic stroke in MMD, it is desirable that the cerebral hemodynamic state should be well evaluated before pregnancy, and treated if severely impaired. In addition, extreme hypertension should be corrected during the perinatal period. Caesarean section is a good choice, but painless vaginal delivery can be also considered.

The present study revealed that fatal stroke can occur if a patient with undiagnosed MMD becomes pregnant. Severe disability or death resulted from hemorrhage rather than ischemia, which is the same result as seen in previous reports.[6] This study also identified a case of intracranial hemorrhage just during vaginal delivery. The relationship between perinatal hypertension and hemorrhagic event is unclear, as detailed data on patient blood pressure were not requested in the questionnaire. In addition, the frequency of perinatal stroke cannot be estimated because it is impossible to determine the number of pregnant women with occult, asymptomatic MMD. Realistically, it appears quite difficult to prevent catastrophic perinatal hemorrhagic stroke from moyamoya vessels if MMD remains undiagnosed. The low prevalence of MMD (6.03 per 100,000 Japanese[7]) and much lower in Western countries) does not justify the screening of all young women with magnetic resonance angiography. At present, the course of action seems limited to taking precautions for pregnancy-induced hypertension and making an accurate diagnosis immediately after the onset of stroke, which enables effective treatment in the acute period.

In Survey II, while some minor events occurred with low frequency, no serious event was detected with pregnancy and delivery in patients with undiagnosed MMD. Although this appears curious at first glance, some reasons can be given for this result. In all but two patients, diagnosis of MMD was made after all births had taken place, and it is unclear whether the onset of MMD predated the births and how severely it affected the patients. In addition, Survey II has the above-mentioned inclusion bias that could be caused by the dropping out of catastrophic cases. Therefore, the risk of undiagnosed MMD-associated pregnancy should not be underestimated.

For any pediatric and young-adult female MMD patient, expected pregnancy is a serious issue. The present study has revealed the current situation, but further research is needed regarding selection of the delivery method, the effect of previous bypass surgery on perinatal stroke prevention, and early diagnosis and clinical management following cerebrovascular events in undiagnosed cases. Furthermore, it should be emphasized that greater coordination among obstetricians, neurologists, and neurosurgeons could help female patients with MMD give birth with greater success. The authors strongly hope that practical guidelines for managing MMD-associated pregnancy are established in the near future.

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Address reprint requests to: Jun C. Takahashi, MD, Department of Neurosurgery, Graduate School of Medicine, Kyoto University, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan.
e-mail: juntak@kuhp.kyoto-u.ac.jp

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DIAGNOSTIC NEURORADIOLOGY

Diagnosis of moyamoya disease using 3-T MRI and MRA: value of cisternal moyamoya vessels

Takeshi Sawada · Akira Yamamoto · Yukio Miki · Ken-ichiro Kikuta · Tomohisa Okada · Mitsunori Kanagaki · Seiko Kasahara · Susumu Miyamoto · Jun C. Takahashi · Hidenao Fukuyama · Kaori Togashi

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Abstract
Introduction The purpose of this study was to propose new magnetic resonance (MR) criteria of diagnosing moyamoya disease (MMD) from cisternal moyamoya vessels (MMVs) on 3-T magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA) and compare the diagnostic accuracy of the existing MR criteria and the proposed MR criteria.

Methods Participants comprised 20 consecutive patients with MMD (4 males, 16 females) diagnosed clinically using conventional angiography and 20 controls (13 male and 7 female arteriosclerosis patients). In these participants, 3-T MRI/MRA was evaluated by the existing MR criteria, which use MMVs in the basal ganglia, and the proposed MR criteria, which use cisternal MMVs, and then these two criteria were statistically compared by McNemar's test.
Results Diagnostic accuracy was 62.5% with the existing MR criteria and 97.5% with the proposed MR criteria. The proposed MR criteria was more sensitive (1.00) than the existing MR criteria (0.45), but less specific (0.95) than the existing MR criteria (1.00).
Conclusion The proposed MR criteria using cisternal MMVs showed significantly higher diagnostic accuracy than the existing MR criteria. We believe that our proposed MR criteria will be beneficial for diagnosing MMD.

Keywords Cisternal moyamoya vessels · Moyamoya disease · Magnetic resonance angiography · Magnetic resonance imaging · T2-weighted imaging

Abbreviations

ACA	Anterior cerebral artery
AUC	Area under the curve
CSF	Cerebrospinal fluid
FSE	Fast spin echo
ICA	Internal carotid artery
MCA	Middle cerebral artery
MIP	Maximum intensity projection
MMD	Moyamoya disease
MMVs	Moyamoya vessels
MR	Magnetic resonance
MRA	Magnetic resonance angiography

T. Sawada · A. Yamamoto (✉) · T. Okada · M. Kanagaki · S. Kasahara · K. Togashi
Department of Diagnostic Imaging and Nuclear Medicine, Graduate School of Medicine, Kyoto University, 54 Shogoin-Kawaharacho, Sakyo-ku, Kyoto 606-8507, Japan
e-mail: yakira@kuhp.kyoto-u.ac.jp

Y. Miki
Department of Radiology, Graduate School of Medicine, Osaka City University, 1-4-3 Asahi-machi, Abeno-ku, Osaka 545-8585, Japan

K. Kikuta
Division of Neurosurgery, Department of Sensory and Locomotor Medicine, Faculty of Medical Sciences, Fukui University, 23-3 Matsuokashimoaizuki, Eiheiji-cho, Yoshida-gun, Fukui 910-1193, Japan

S. Miyamoto · J. C. Takahashi
Department of Neurosurgery, Graduate School of Medicine, Kyoto University, 54 Shogoin-Kawaharacho, Sakyo-ku, Kyoto 606-8507, Japan

H. Fukuyama
Human Brain Research Center, Graduate School of Medicine, Kyoto University, 54 Shogoin-Kawaharacho, Sakyo-ku, Kyoto 606-8507, Japan

MRI	Magnetic resonance imaging
ROC	Receiver operating characteristic
SNR	Signal-to-noise ratio
SWI	Susceptibility-weighted imaging
T2WI	T2-weighted imaging
TOF	Time-of-flight

Introduction

Moyamoya disease (MMD) is a relatively rare disorder in which distal portions of the internal carotid arteries (ICAs) and/or proximal portions of the anterior cerebral artery (ACA) and/or middle cerebral artery (MCA) become progressively steno-occlusive with secondary formation of collateral vessels and abnormal vascular network called moyamoya vessels (MMVs) [1]. This disease occurs predominantly in Japanese, but occurrence has also been reported in other countries [2, 3]. The etiology of MMD has been unknown for long, but recently, its responsible genes are being identified [4]. There are reported links between moyamoya-like state and a wide variety of other disorders such as radiation arteritis, Down's syndrome, and so on; they are excluded clinically [5]. By the finding of conventional angiography, disease severity is frequently classified into one of six progressive stages (Suzuki's stage) [1]. MMD is well known to cause transient ischemic attacks, cerebral infarction, or intracranial bleeding in both children and adults [6, 7]. Intracranial bleeding, in particular, often results in poor outcomes [1]. Cases with relatively mild and slow progression are usually treated more conservatively, while cases with faster progression are treated surgically, such as with vascular bypass methods [2]. Treatment of MMD depends on the possibility of faster deterioration, so frequent follow-up imaging as well as accurate diagnosis and staging of the disease on each examination is indispensable in the clinical situation.

MMD has been diagnosed using diagnostic criteria that apply results from conventional angiography and magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA) independently [5]. In the existing guideline, conventional angiography still remains to be the gold standard for the diagnosis of MMD in principle [8, 9], and the relatively large number of patients that do not fulfill the diagnostic criteria from MRI/MRA need diagnostic conventional angiography [5, 10, 11]. Conventional angiography can visualize stenosis of both normal vessels and MMVs more clearly and definitively, therefore enabling more precise evaluation of vessels, which is necessary for surgical treatment. One drawback of the existing diagnostic criteria using conventional angiography is the possibility of unwanted side effects such as contrast media allergy which might be serious in some cases [12]. Another drawback of the existing diagnostic criteria is the technical difficulty of conventional angiography in pediatric cases due to the narrow artery and need for sedation.

Nowadays, 3-T magnetic resonance (MR) is widely used in clinical situations and has been reported to show superiority to 1.0/1.5-T MR in the diagnosis of various neurological disorders [13–15]. The higher spatial resolution and signal-to-noise ratio (SNR) of 3-T MR are useful for evaluating the fine features of MMD. MMVs have been reported to be better delineated with MRA at 3-T than at 1.5-T [15]. For microbleeds in MMD, representing an important factor for prognosis [16], susceptibility-weighted imaging (SWI) has been reported to offer better detection at 3-T than 1.5-T MRI [17]. In the clinical situation, MRI/MRA findings have been used for the diagnosis of MMD, such as cisternal MMV and the fluid-attenuated inversion recovery ivy sign [18, 19]. Among these fine features of MMD, the cisternal MMVs visualized as a distinct feature of MMD on 3-T MR might be beneficial for diagnosing MMD. These fine features of MMD visualized by recent MR technique have been available by now; therefore, an updated guideline which reflects these benefits has been needed. This study proposes new diagnostic criteria for MMD using cisternal MMVs evaluated by routine clinical 3-T MRI/MRA. We hypothesized that the proposed MR diagnostic criteria using 3-T MR can diagnose MMD more accurately by evaluating cisternal MMVs than the existing MR criteria, which evaluates MMVs in the basal ganglia. The purpose of this study was to evaluate the diagnostic accuracy of the proposed MR criteria and the existing MR criteria using 3-T MRI/MRA.

Materials and methods

Patients

All study protocols were approved by the local ethics committee and written informed consent was obtained from all patients or their parents. The study included 20 consecutive patients with MMD from March 2004 to April 2008 (4 males, 16 females; mean age, 26.3 years; range, 2–58 years) and 20 controls (13 male and 7 female arteriosclerosis patients; mean age, 64.7 years; range, 27–87 years). All MMD patients had been diagnosed clinically using the existing diagnostic criteria, including conventional angiography. Suzuki's stages of MMD patients are shown in Table 1. Cases of unilateral MMD were not included in this study. Control arteriosclerosis patients showed multivessel stenosis. Four cases showed greater than or equal to three vessel stenoses, eight cases showed two vessel stenoses, and eight cases showed stenosis of one vessel.

Table 1 The diagnostic category of MMD patients and controls

		Existing MR criteria	Proposed MR criteria	Suzuki's stage	
Age (years), sex	Diagnosis	Category	Category	Right	Left
2, F	MMD	4	5	4	4
6, F	MMD	3	5	3	4
6, F	MMD	2.5	4.5	3	2
7, F	MMD	2	5	2	3
8, F	MMD	3	5	2	4
8, M	MMD	5	5	4	4
13, F	MMD	1	5	2	3
14, F	MMD	1	5	2	2
21, F	MMD	1	4.5	2	2
21, F	MMD	2.5	5	4	4
22, F	MMD	1	5	4	4
31, F	MMD	2	5	3	3
32, F	MMD	1	5	3	2
35, F	MMD	1	4	2	2
47, F	MMD	3	5	3	3
48, F	MMD	1	5	4	3
49, F	MMD	1	5	3	3
49, M	MMD	1	4.5	2	2
50, M	MMD	1	5	3	3
58, M	MMD	1	5	3	3
27, M	CTR	1	4		
30, M	CTR	1	1		
41, F	CTR	1	1		
42, F	CTR	1	1		
61, F	CTR	1	1		
65, M	CTR	1	1		
66, M	CTR	1	1		
66, M	CTR	1	1		
66, M	CTR	1	1		
69, F	CTR	1	1		
70, F	CTR	1	1		
73, M	CTR	1	1		
74, M	CTR	1	1		
74, F	CTR	1	1		
76, M	CTR	1	2.5		
76, M	CTR	1	1		
76, F	CTR	1	1		
77, M	CTR	1	1		
78, M	CTR	1	1		
87, M	CTR	1	1		

MMD moyamoya disease, *CTR* control

Image acquisition

All patients and controls underwent 3D time-of-flight (TOF) MRA and fast spin echo (FSE) T2-weighted imaging (T2WI) using a 3-T MR scanner (Magnetom Trio; Siemens, Erlangen, Germany). A dedicated head array coil was used for image acquisition. The following parameters were used for TOF MRA: repetition time, 22 ms; echo time, 3.7 ms; flip angle, 20°; slice thickness, 0.7 mm; slab thickness, 33.6 mm; number of slabs, 3; field of view, 200×150 mm; matrix, 320×240; voxel size, 0.625×0.625×0.7 mm; and acquisition time, 5 min 51 s. The following parameters were

used for FSE T2WI: repetition time, 3,200 ms; echo time, 79 ms; echo trains per slice, 14; slice thickness, 3 mm; slice gap, 1 mm; field of view, 220×176 mm; matrix, 448×360; voxel size, 0.6×0.5×3 mm; and acquisition time, 1 min 44 s.

Diagnostic methods

The existing MR criteria for the diagnosis of MMD using MRI/MRA [5] and the proposed MR criteria for the diagnosis of MMD using 3-T MRI/MRA are shown in Table 2 and Figs. 1 and 2.

In the Sylvian valley, T2WI shows cisternal MMVs as worm-like structures and a network of numerous randomly formed flow voids in axial slices (Fig. 3). Source images from TOF MRA also show MMVs as a network of numerous randomly formed high signal intensity structures in the cisternal low signal intensity (Fig. 4). In this study, cisternal MMVs were evaluated on T2WI and TOF MRA with source images.

Image evaluation

Two board-certified neuroradiologists (T.S. and A.Y. with over 8 years of experience) evaluated T2WI and TOF MRA using the existing and proposed MR criteria. Evaluation based on MRI/MRA for each side was classified into five categories (5, absolutely positive; 4, probably positive; 3, unclear; 2, probably negative; and 1, absolutely negative).

The procedure for evaluation using the existing MR criteria is as follows: (a) evaluation of whether stenosis exists at the ICA, ACA, and/or MCA on the right side; (b) evaluation of MMVs in the basal ganglia on T2WI (Fig. 2) on the right side; and (c) repetition of the same evaluations for the left side.

Table 2 The existing and proposed MR criteria for diagnosing MMD

The existing MR criteria [5]
When MRI and MRA clearly demonstrate all the below findings, conventional cerebral angiography is not mandatory.
1. Stenosis or occlusion at the terminal portion of the ICA and/or at the proximal portion of the ACA and/or the MCA (Fig. 1).
2. An abnormal vascular network in the basal ganglia on MRA. An abnormal vascular network can be diagnosed when more than two flow voids are seen on one side of the basal ganglia on MRI (Fig. 2).
3. Bilateral appearance of 1 and 2.
The proposed MR criteria
1. Stenosis or occlusion at the terminal portion of the ICA and/or at the proximal portion of the ACA and/or the MCA (Fig. 1).
2. An abnormal vascular network of cisternal MMVs apparent in bilateral Sylvian valleys on T2WI or MRA (Figs. 3 and 4).
3. Bilateral appearance of 1 and 2.

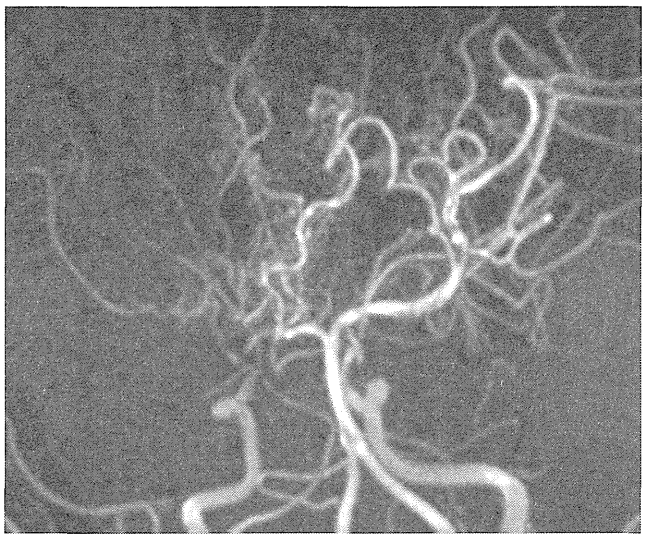

Fig. 1 MRA maximum intensity projection (MIP) of MMD showing stenosis of bilateral ICAs

The procedure for evaluation using the proposed MR criteria is as follows: (a) evaluation of whether stenosis exists at the ICA, ACA, and/or MCA on the right side; (b) evaluation of MMVs in the Sylvian valley (Figs. 3 and 4) on the right side; and (c) repetition of the same evaluation on the left side.

In this study, evaluation was performed on the right and left sides separately because the degree of stenosis of arteries and formation of MMVs are not symmetrical in all MMD patients [20]. In the existing MR criteria and the proposed MR criteria, the concordance rate of the scores by the two neuroradiologists was evaluated by the kappa coefficient. If the scores for each side did not fully agree, the scores were decided by consensus. The diagnostic category for the patient was defined as the average of category scores

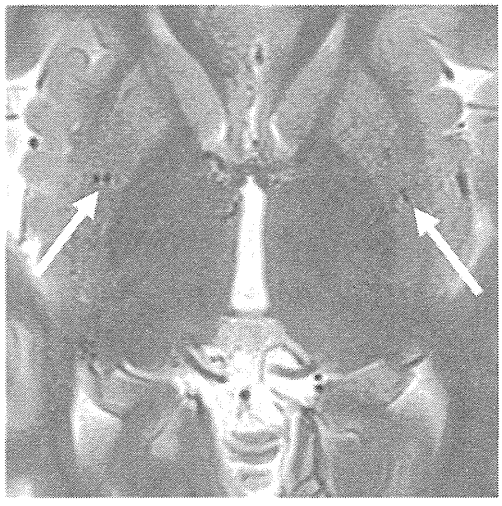

Fig. 2 Axial FSE T2WI shows MMVs at the level of the basal ganglia. Flow voids indicating abnormal vascular networks are visualized at bilateral putamina

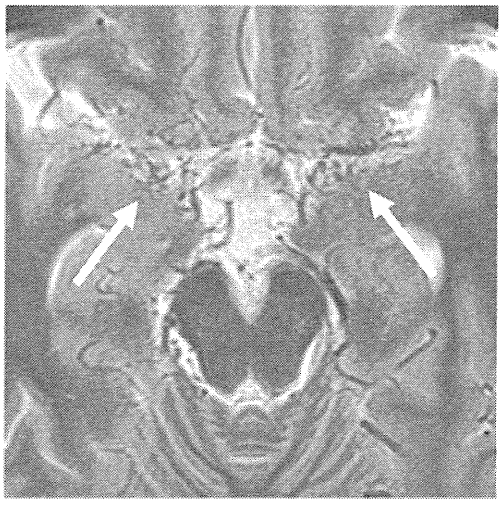

Fig. 3 Axial FSE T2WI shows MMVs at the level of the Sylvian valley. Flow voids of MMVs were apparent in bilateral Sylvian valleys

of the left and right sides. Sample images of an MMD patient are shown in Fig. 5. The diagnostic category by the existing MR criteria was 1, and that by the proposed MR criteria was 5.

Statistical analysis

As the first analysis, receiver operating characteristic (ROC) curves for both the existing and proposed MR criteria were used for statistical evaluation of diagnostic accuracy. Area under the curve (AUC) for each criteria was then calculated and comparisons of diagnostic accuracy for the existing and proposed MR criteria were performed using Hanlay's method, with values of $p<0.05$ considered significant [21].

As the second analysis, cutoff points were calculated for each criteria to maximize sensitivity and specificity. Using these cutoff points for each criteria, diagnostic accuracies of the two criteria for clinical diagnosis were calculated according to results from conventional angiography and compared using McNemar's test [22].

As the third analysis, to avoid calculation bias from comparing two criteria with separate cutoff points, a common cutoff point was determined at the median of the range (category 3). Categories <3 were considered as not MMD and categories ≥3 were considered as MMD, with category 3 included in MMD to maximize the sensitivity of the diagnostic method. With this common cutoff point, diagnostic accuracies of the two criteria for clinical diagnosis using conventional angiography were calculated and compared using McNemar's test [22].

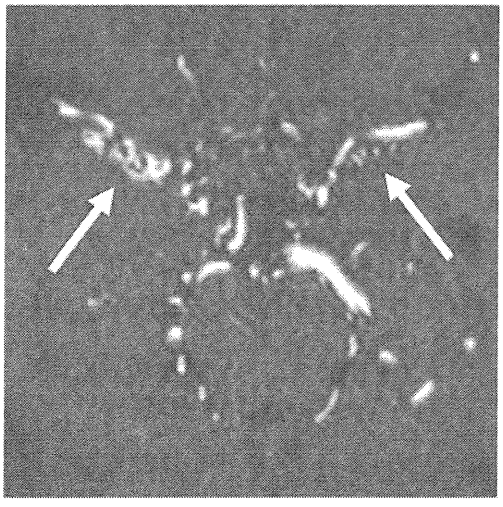

Fig. 4 MRA source image also shows MMVs at the level of the Sylvian valley. MMVs were apparent in bilateral Sylvian valleys as high signal intensity

Results

The kappa coefficient of the scores of the two neuroradiologists by the existing MR criteria was 0.63, and that by the proposed criteria was 0.89. ROC curves for the two criteria are shown in Fig. 6. The diagnostic categories for MMD patients and controls are shown in Table 1. Standard deviations for the existing MR criteria were 0.71 in MMD patients and 0 in controls, and those for the proposed MR criteria were 0.26 in MMD patients and 1.16 in controls. Median values for the existing MR criteria were 1 in MMD cases and 1 in controls, and those for the proposed MR criteria were 5 in MMD patients and 1 in controls.

AUC of the existing MR criteria was 0.725 (two-sided 95% confidence interval, 0.567–0.883). AUC of the proposed MR criteria was 0.999 (two-sided 95% confidence interval, 0.988–1.000). A comparative test using Hanlay's method showed that the difference of the two AUCs was 0.274, with a standard error of 0.080 and a correlation coefficient between the two AUCs of 3.403. A significant difference between the two criteria was identified ($p=0.0007$).

In the second analysis, cutoff points were calculated for each criteria to maximize sensitivity and specificity using ROC curves. The cutoff point for the existing MR criteria was 1.5 (sensitivity, 0.45; specificity, 1.00), compared to 3.25 (sensitivity, 1.00; specificity, 0.95) for the proposed MR criteria. Using conventional angiography as the gold standard, accuracies of the two criteria with each cutoff point were 72.5% for the existing MR criteria and 97.5% for the proposed MR criteria. McNemar's test showed a significant difference between the two criteria ($p=0.006$).

In the third analysis, the cutoff point for the existing and proposed MR criteria was the common cutoff point of 3. Using conventional angiography as the gold standard, accuracies of the two criteria with the common cutoff point were 62.5% for the existing MR criteria and 97.5% for the

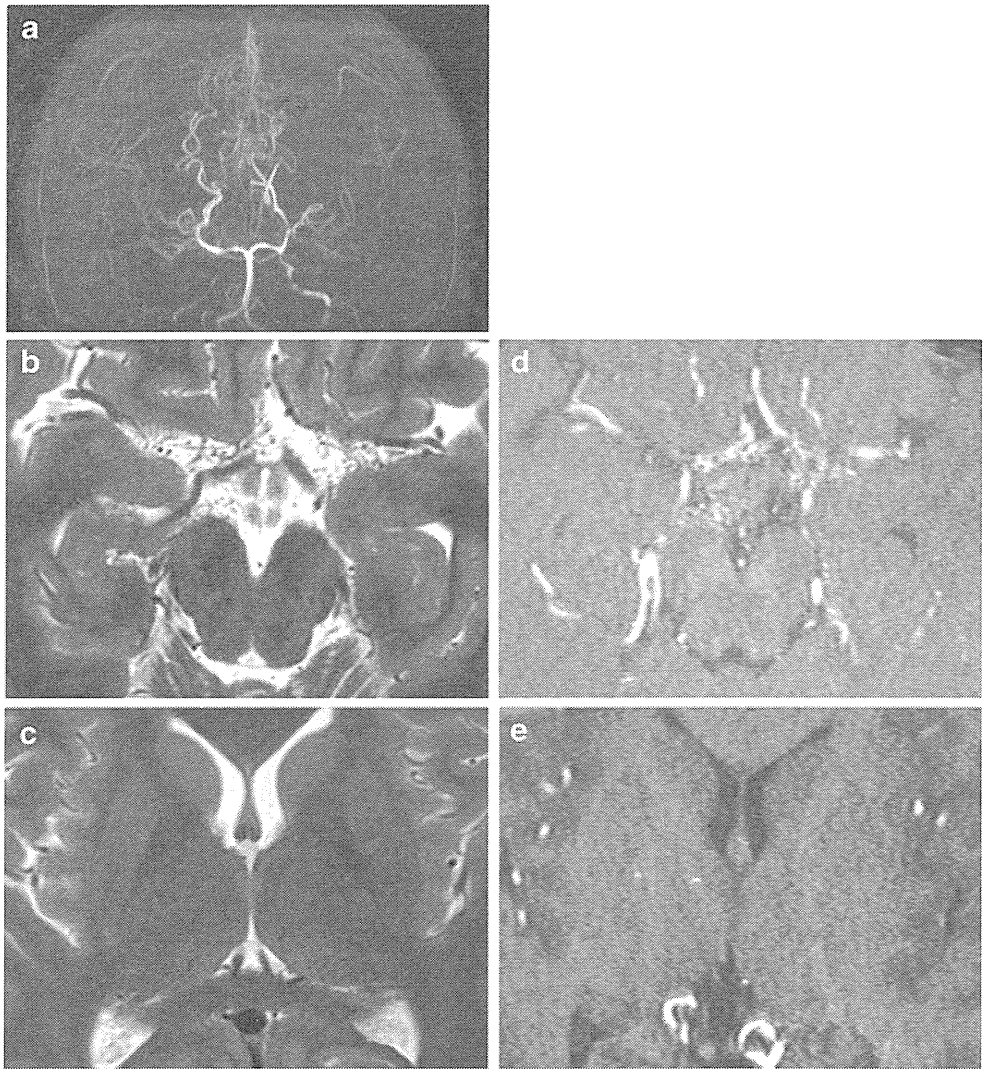

Fig. 5 MRA MIP, T2WI, and MRA source images from a patient with MMD (category 5 by the proposed MR criteria; category 1 by the existing MR criteria). **a** MRA MIP. **b** T2WI at the level of the Sylvian valley. **c** T2WI at the level of the basal ganglia. **d** MRA source image at the level of the Sylvian valley. **e** MRA source image at the level of the basal ganglia

proposed MR criteria. McNemar's test showed a significant difference between the two criteria (p=0.001).

The results of the second and third analyses are also shown in Table 3.

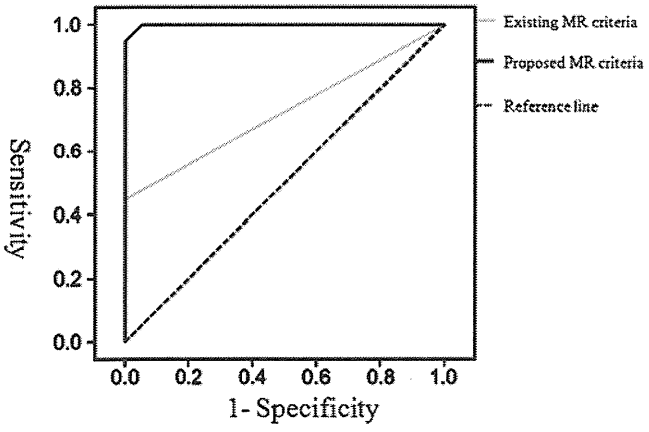

Fig. 6 ROC curves of the two criteria

Discussion

This study evaluated 3-T MRI/MRA in 20 MMD patients and 20 controls using the existing and proposed MR criteria for the diagnosis of MMD. AUC of ROC curves for these two criteria showed a significant difference. Accuracies of the existing and proposed MR criteria showed a significant difference according to McNemar's test using each cutoff point and common cutoff point. The proposed MR criteria using 3-T MRI/MRA showed superior diagnostic accuracy for MMD.

The existing diagnostic criteria of MMD were defined by the Research Committee on Spontaneous Occlusions of the Circle of Willis (MMD) of the Ministry of Health and Welfare of Japan in 1997 [5]. At that time, 1.0- or 1.5-T MR was widely used and 3-T MR was not widely available in clinical situations. In the evaluation of MMD patients, features of vessels delineated by MRI/MRA using 1.0/1.5-T MR might be suboptimal for definitive diagnosis in more than a few cases [11]. Substantial cases were unable to be

Table 3 The results of the second and third analyses

		Cutoff point	Sensitivity	Specificity	Accuracy (%)
Second analysis	Existing MR criteria	1.5	0.45	1.00	72.5
	Proposed MR criteria	3.25	1.00	0.95	97.5
Third analysis	Existing MR criteria	3			62.5
	Proposed MR criteria				97.5

diagnosed using MRI/MRA alone, so conventional angiography has been required as the gold standard for definite diagnosis of MMD in not a few patients, including pediatric cases [23].

If the definite standard with high accuracy of diagnosis using the relatively less-invasive MR had settled, more patients could skip conventional angiography. This would prove beneficial for MMD patients, particularly for children. Several studies have discussed the diagnosis of MMD using MRI/MRA, mainly using 1.5-T MR [11, 24–27]. Although 1.5-T MR can be used for diagnosing MMD in the clinical setting, the accuracy of diagnosis has been suboptimal due to the intrinsic difficulties of acquiring higher spatial resolution and higher SNR [28]. In many cases, conventional angiography has been used as the gold standard for the clinical diagnosis of MMD under the existing diagnostic criteria [8–10].

Cisternal MMVs, one of the fine features of MMD, are defined as tortuous small vessels in the Sylvian valley other than the MCA and its perforators and are visualized as worm-like structures on axial slices in MRI/MRA [18, 29] (Figs. 3 and 4). These cisternal MMVs have been visualized using high-resolution T2WI with constructive interference in steady-state imaging on 1.5-T systems and may be beneficial in diagnosing MMD using MRI [30]. However, this sophisticated technique requires a relatively long scan time and has thus been difficult to use in screening and frequent follow-up examinations.

Nowadays, 3-T MR has been introduced widely into clinical situations. Various features of MMD have been reported to be more clearly apparent with 3-T MR than with 1.5-T MR, including vascular abnormalities on MRA and microbleeds on SWI [15, 17]. Some reports have noted that 3-T MRI/MRA visualizes more fine features of MMVs than MRI/MRA at 1.0/1.5-T [14, 15]. As 3-T MRI offers a higher SNR than 1.0/1.5-T MR, a higher spatial resolution on T2WI can be achieved. Also, 3-T MR has a longer longitudinal relaxation time than 1.0/1.5-T MR, allowing improved T1 contrast and a higher signal on TOF MRA. These superior properties of 3-T MRI/MRA might have performed a significant role in improving the accuracy of diagnosing MMD in this study.

With the existing MR criteria, MMV is evaluated as flow voids in the basal ganglia on T2WI. On routine clinical 3-T MR images, flow voids in the basal ganglia may be difficult to detect. Compared to 1.5-T MRI, the basal ganglia sometimes show as areas of low signal intensity on 3-T MRI due to the rich iron content [31], so low-signal flow voids might be difficult to detect in the basal ganglia. Conversely, with the proposed MR criteria, MMVs were steadily evaluated in the Sylvian valley where low-signal vascular flow voids are more readily apparent against the background of high signal intensity cerebrospinal fluid (CSF) on T2WI [29]. In addition, 3-T MRA showed MMVs more clearly in both the basal ganglia and Sylvian valley due to the longer longitudinal relaxation time [15]. In the present study, T2WI and MRA were evaluated together in both the existing and proposed MR criteria, which may prevent influences of artifacts such as CSF flow void in the Sylvian valley complementarily and facilitate evaluation of the fine features of MMVs in the proposed MR criteria.

If MMD can be definitively diagnosed using only 3-T MRI/MRA, conventional angiography can be skipped. This may be beneficial for the first diagnosis of MMD, as the procedure for conventional angiography can have unwanted side effects [12]. In addition, this may be beneficial for patients with slow progression, who can be followed up using MRI/MRA alone and treated conservatively without surgical therapy unless frequent imaging examinations show deterioration [32]. Diagnosis of MMD using 3-T MRI/MRA alone may thus be beneficial for accurate first diagnosis and subsequent imaging follow-ups for early treatment [33, 34].

Several limitations must be considered when interpreting the results of this study. First, age-matched controls were not enrolled in the study. This is because MMD patients in this study were younger than the control patients with arteriosclerosis. The incidence of MMD shows peaks in two age groups: children at approximately 5 years old and adults in their mid-40s [3, 35]. Second, we used cisternal MMVs in the Sylvian valley for diagnosis, but MMVs do not become obvious at stage 1 and vanish at stages 5 and 6 [1]. The proposed MR criteria may not work in such low-stage and higher-stage cases. Suzuki's stages 1 and 2 are considered as the early stages of MMD. Stages 3 and 4, which are the most frequently observed stages, are clinically important and have to be clinically discriminated. Suzuki's stages 5 and 6 are considered as the final stages of MMD [1, 35]. And onset of the disease at stage 5 or 6 is rare, so evaluation of cisternal MMVs may be feasible in many cases. Diagnosis of stage 1 cases by MRI/MRA is one of our future tasks and under way.

Conclusion

This study evaluated the accuracy of the proposed MR criteria for diagnosing MMD using cisternal MMVs visualized by 3-T MRI/MRA. The diagnostic accuracy of the proposed MR criteria was higher than that of the existing MR criteria. We believe that the proposed MR criteria using 3-T MRI/MRA will prove beneficial for diagnosing MMD.

Conflict of interest We declare that we have no conflict of interest.

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もやもや病における
高次脳機能障害に関する検討
COSMO-JAPAN study
(Cognitive dysfunction Survey of Moyamoya)

暫定プロトコール

2013. 5. 1

厚生科学研究費特定疾患対策研究事業

もやもや病（ウィリス動脈輪閉塞症）の治療・診断に関する研究

研究代表者

橋本　信夫

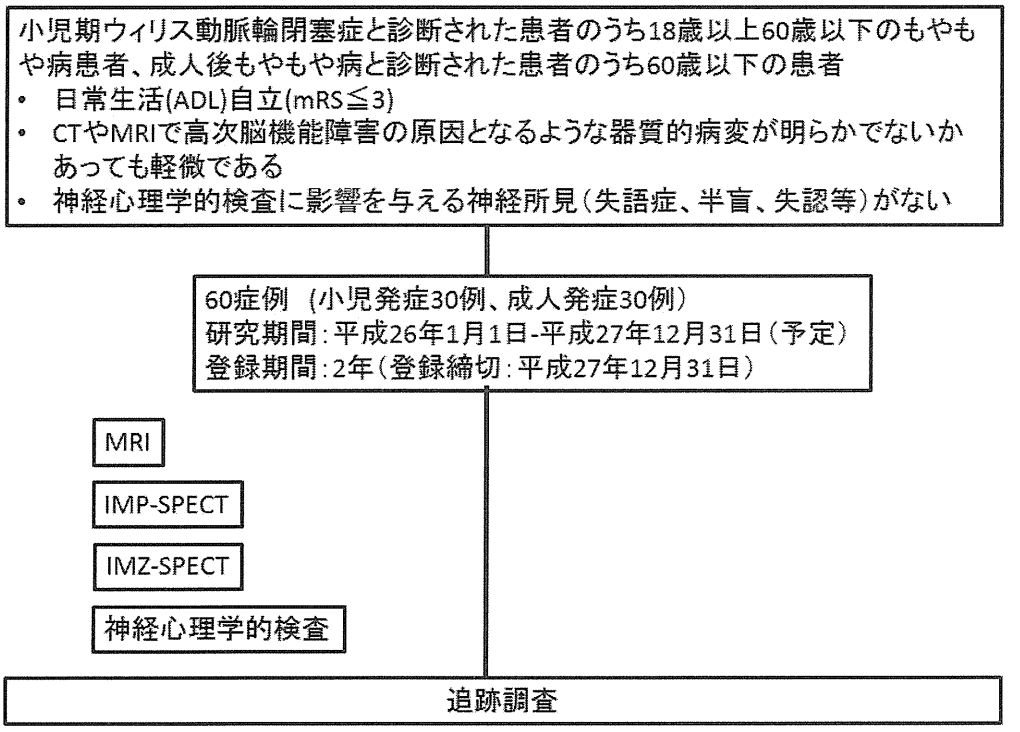
（国立循環器病研究センター　理事長）

COSMO-JAPAN study
主任研究者

宮本　享
（京都大学　医学研究科　脳神経外科）

0. 概　要

0.1. フローチャート



0.2. 目　的

高次脳機能障害の原因となるような器質的病変が明らかでないかあっても軽微な症例における画像診断法と神経心理学的検査を確立することが本研究の目的である

0.3. 登録基準

小児期ウィリス動脈輪閉塞症と診断された患者のうち 18 歳以上 60 歳以下のもやもや病患者、成人後もやもや病と診断された患者のうち 60 歳以下の患者

- 日常生活(ADL)自立(mRS≦3)
- CT や MRI で高次脳機能障害の原因となるような器質的病変が明らかでないかあっても軽微である
- 神経心理学的検査に影響を与える神経所見（失語症、半盲、失認等）がない

0.4. 目標登録症例数

60 症例　(小児発症 30 例、成人発症 30 例)

0.5. 研究期間

登録期間：2年

0.6. 研究デザイン

多施設共同登録観察研究

0.7. 連絡先

主任研究者

宮本　享

京都大学医学研究科　脳神経外科

〒606-8507 京都市左京区聖護院川原町 54

Tel 075-751-3459 Fax 075-752-9501

研究事務局

高木康志

京都大学医学研究科　脳神経外科

〒606-8507 京都市左京区聖護院川原町 54

Tel 075-751-3459 Fax 075-752-9501

E-mail　ytakagi@kuhp.kyoto-u.ac.jp

森井香代子（担当秘書）

E-mail　kayokom@kuhp.kyoto-u.ac.jp

本研究実施計画書は、本研究に直接かかわる者および倫理審査委員会以外の者に情報を開示してはならない。また、本情報は事前の書面による主任研究者の承諾なしに本件の実施あるいは評価以外の目的に利用してはならない。

本研究に関与する全ての者は「世界医師会ヘルシンキ宣言」および「臨床研究に関する倫理指針」に従う。

1. 背　景

ウィリス動脈輪閉塞症（もやもや病、以下本疾患）は1960年代にわが国で発見されて概念が確立された疾患である。本疾患は両側内頚動脈終末部を中心に進行性の閉塞が生じる原因不明の疾患である。東アジアを中心に小児、成人両者に発生するのが特徴で、一部には家系内発生も認められる。大部分の小児は脳虚血発作（一過性脳虚血発作および脳梗塞）で発症するが、成人では脳虚血発作に加えて頭蓋内出血で発症することが特徴である。これまでの研究によって、脳血行再建術は脳虚血発作の再発を予防して長期予後を改善させることが判明している。

一方、高次脳機能障害の定義は高次脳機能障害診断基準によると「脳の器質的病変の原因となる事故による受傷や疾病の発症により、日常生活または社会生活に制約が生じ、その主たる要因が、記憶障害、注意障害、遂行機能障害、社会的行動、障害などの高次の認知障害」とあり、その原因として外傷、脳血管障害、その他と記載されている。高次脳機能障害の症状は多種多様で、記憶・注意力の低下、言語障害、遂行機能障害、社会的行動障害などの認知障害などが一般的で、脳の損傷箇所や程度によって大きく異なる。また、感情や行動の抑制力が低下するなどの精神・心理的症状も現れ、正しい判断ができなくなる症例もあり社会問題となっている。特に前頭葉に起因する症状は、専門家による神経心理テストにより診断する必要があり、診断に苦慮することが多いことが報告されている。本疾患においては、これまでに前頭葉内側面の神経細胞の脱落がSPECT を用いた解析で示唆され（Neurol Med Chir (Tokyo). 2012)、また成人例でStroke の既往のない症例においても23%に神経心理学的検査で異常を認めたとの報告がある（Neurosurgery. 2012)。しかし、いずれも少数例での報告であり、まとまった症例数の解析ではない。また、精神障害者保健福祉手帳の取得には原則として脳器質性障害を示す画像診断が必要であり、新たな画像診断法の確立は社会的にも急務である。そこでこの度、日本全国で、これまでの conventional な画像診断による器質障害の軽度な症例において、前頭葉機能に focus した神経心理学的検査を行うとともに、Iomazenil SPECT と MRI による新たな診断法の確立を目指したもやもや病における高次脳機能障害に関する検討 COSMO·JAPAN study(Cognitive dysfunction Survey of Moyamoya)が計画された。

2. 目　的

高次脳機能障害の原因となるような器質的病変が明らかでないかあっても軽微な症例における画像診断法と神経心理学的検査を確立することが本研究の目的である。

3. 対　象

3.1. 選択対象

以下の全てを満たす患者を本研究の対象とする

(1) 本研究への参加に同意した日に年齢が 18 歳以上 60 歳未満である患者

(2) 神経放射線学的に両側または片側ウィリス動脈輪閉塞症（もやもや病）と確定診断された患者

(3) 確定診断までに頭蓋内出血（脳出血、脳室内出血あるいはクモ膜下出血）のエピソードを有していない患者（ただし微少出血および脳実質に影響のない脳室内出血は除く）

(4) 画像診断にて大きな器質的病変（1 cortical artery の支配領域以上の病変）を指摘できない患者

(5) 神経心理学的検査に大きな影響を与える神経所見（失語症、半盲、失認等）を有していない患者

(6) 日常生活がほぼ自立している（modified Rankin scale 0ー3）患者

(7) 自覚あるいは他覚症状、日常生活状況から高度な高次脳機能障害の存在が疑われる患者（片麻痺等の神経学的脱落症状が原因の場合は除く）

(8) 十分なインフォームド・コンセントによる研究参加への同意が得られている患者（未成年の場合は親権者）

＊確定診断までに脳虚血症状のエピソードを有しているかどうかは問わない。

＊血行再建術の既往の有無は問わない。

3.2. 除外基準

以下の基準のいずれかを満たす患者は本研究の対象としない

(1) 類もやもや病である患者

(2) 体内の金属などにより MRI の実施が困難である患者

(3) 画像判定委員会にて、もやもや病ではないと判定された患者

(4) そのほか、研究担当医師が不適格と判断した患者

4. 実施要項

4.1. 研究デザイン

多施設共同登録観察研究

4.2. 医師の研究参加

参加を意図する医師が所属する施設の倫理委員会の承認および施設長の許可を得る必要がある。

4.3. 症例登録

担当医：病状説明を十分に行なって文書によるインフォームド・コンセントを得る
登録票に記入して事務局へ FAX で送付する（別途配布）

↓

事務局：登録票より適格性を確認、その結果を FAX で担当医に返信する
（その際は研究固有番号を付与する）

↓

担当医：適格であれば、画像を含めた登録時データを事務局に送付する
（その際は研究固有番号を使用し、個人情報は利用しない）

↓

事務局：送付された画像を委員会で判定して、当該患者は適格であるか最終判断する
結果を担当医に通知する

＊ 症例登録用のファイル(別途配布)に必要事項を記入して画像データを含む CD-R とともに下記の研究事務局に郵送する。

高木康志
〒606-8507 京都市左京区聖護院川原町 54　京都大学　脳神経外科
Tel: 075-751-3459 Fax:075-752-9501
E-mail: ytakagi@kuhp.kyoto-u.ac.jp
森井香代子（担当秘書）
E-mail: kayokom@kuhp.kyoto-u.ac.jp

4.4. 経過観察

本研究期間中は、十分な注意深い観察を行う。内科治療については、抗血小板剤、抗てんかん剤は必須ではなく、その使用は研究責任医師あるいは研究分担医師の方針に委ねる。高血圧、糖尿病、脂質代謝異常などの内科疾患があれば適切な治療を実施すべきである。その際は、保険診療内で実施し、手術適応があれば手術を行っても良い。