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2. Unilateral cases

1) Definition

Unilateral moyamoya disease is also referred to as probable moyamoya disease and refers to the presence of unilateral stenosis or occlusion of the terminal portion of the internal carotid arteries accompanied by the formation of moyamoya vessels around that region. These unilateral changes may occur concurrently with other underlying diseases, such as hyperthyroidism, intracranial arteriovenous malformation, Down‟s syndrome, Apert‟s syndrome, von Recklinghausen‟s disease, postirradiation of the head, SLE and Sjögren‟s syndrome; when these underlying diseases are present, the condition is classified as quasi-moyamoya disease and not as unilateral moyamoya disease[1]. In children, when there is a stenosis of the terminal portion of the internal carotid arteries on the other side also, it should be included as definitive moyamoya disease and not as unilateral moyamoya disease[2].

2) Epidemiology

In a primary survey conducted in 2,998 Japanese institutions in 2006, the frequency of unilateral moyamoya disease was 10.6% among 2,635 patients with moyamoya disease, including initially diagnosed and re-diagnosed patients[3]. A family history is occasionally present for patients with unilateral moyamoya disease [4]. An analysis of 15 families having a family history of the disease in 3 or more generations revealed 5 patients with concurrent unilateral moyamoya disease in addition to 43 patients with definitive moyamoya disease , and suggested the possibility that the disease was inherited by the same autosomal dominant inheritance pattern. Because of this, unilateral moyamoya disease with a family history is also viewed as a subtype of moyamoya disease [5]. In addition, unilateral moyamoya disease is also distinguished from definitive moyamoya disease without a positive family history or increased bFGF levels in the cerebrospinal fluid[6].

3) Symptoms and diagnostic methods

The symptoms of unilateral moyamoya disease are basically the same as those of the patients with definitive moyamoya disease. In addition to cerebral ischemic symptoms[7], cerebral hemorrhage[8], concurrent cerebral aneurysm[9], involuntary movement[10], etc., may be noted. A definitive diagnosis is made based on cerebral angiography, and the severity of cerebral ischemia is determined by brain perfusion scintigraphy[11].

4) Progression from unilateral to bilateral moyamoya disease

The reported frequency of progression from unilateral to bilateral moyamoya disease varies from 10 to 39% among reports. In a study where 10 patients with unilateral moyamoya disease were followed up for 10 years, the condition progressed to bilateral disease in only 1 (10%) pediatric patient; thus, progression to bilateral disease appears to be rare[6]. In another study conducted on children, however, a unilateral condition progressed to bilateral disease in 2 of 6 patients (33%) [12] and in a study of 64 patients with unilateral moyamoya disease followed up for 1 to 7 years, progression to bilateral disease was noted in 17 (27%) patients, and such progression to bilateral disease within 5 years was frequent in children with early-onset of moyamoya disease (age at onset 10 years or less)[13]. In a follow-up study of 12 pediatric patients and 5 adult patients, progression to bilateral disease was noted in only 6 (39%) pediatric patients during a 20-month follow-up period[14].

In contrast, in a recent follow-up study of 28 patients with unilateral moyamoya disease, the condition progressed to bilateral disease in 7 (25%) patients, and 5 of these patients were adults. Thus, progression to bilateral disease may be noted not only in pediatric patients, but also in adult patients. The statistically significant risk factors for progression to bilateral disease have been suggested to be the presence of equivocal or mild stenotic changes in the internal carotid artery, middle cerebral artery or anterior cerebral artery of the other side[15].

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CHAPTER VI. DIAGNOSIS

1. Cerebral angiography, MRI, etc.

1) Recommendations

Cerebral angiography is essential for a definitive diagnosis of moyamoya disease (Diagnostic criteria, P.1)[1].

In MRI, a definitive diagnosis can be made when the following findings are fulfilled on Time of Flight (TOF) imaging conducted using a device with a magnetostatic intensity of $\frac{24}{12}$ 1.5 **T** (especially 3.0 tesla)[1-4]:

(1) On MRA, stenosis or occlusion of the terminal portion of the intracranial internal carotid artery or proximal portion of the anterior and/or middle cerebral arteries.
(2) On MRA, abnormal vascular networks in the basal ganglia. (Note) When 2 or more visible flow voids in the basal ganglia are present at least unilaterally on MRI, they can be deemed as representing an abnormal vascular network.
(3) Bilaterality of findings (1) and (2).

Stage classification can be also made based on the MR findings in some cases; it can be performed in consideration of the safety of examination (C1)[1].

2) Explanation

In principle, the diagnosis of moyamoya disease is made based on

(1) stenosis or occlusion of the terminal portion of the intracranial internal carotid artery or the proximal portion of the anterior and/or middle cerebral arteries;
(2) abnormal vascular networks in the vicinity of the occlusive or stenotic lesions in the arterial phase; and
(3) bilaterality of findings (1) and (2).

Cerebral angiography is essential for the diagnosis, but when the above MR findings are present, they are, as an exception, recognized as diagnostic criteria (III). However, the above diagnostic criteria should be considered as the standard for designation as an intractable disease by the Ministry of Health, Labour and Welfare. When assuming surgical treatment, conventional cerebral angiography should be performed as far as possible (III)[1].

Stage classification based on the cerebral angiographic findings is well known (Table 1)[5, 6].

On the other hand, a classification based on the MRA findings has been proposed (Table 2)[7]. In this system, the stage is determined by simply assigning scores to the MRA findings and then totaling the scores. The stage classification using this method corresponds well to the conventional classification based on angiography, and has been reported to have a high sensitivity and specificity (III)[7].

MRA stage 1 identified using the above approach corresponds to stages I and II of the angiographic classification, stage 2 corresponds to stage III, stage 3 corresponds to stage IV, and stage 4 corresponds to stages V and VI; the classification is thus practical (III)[7].

Table 1 Stage classification

Stage I	Narrowing of the carotid fork
Stage II	Initiation of the moyamoya (dilated major cerebral artery and a slight moyamoya vessel network)
Stage III	Intensification of the moyamoya (disappearance of the middle and anterior cerebral arteries, and thick and distinct moyamoya vessels)
Stage IV	Minimization of the moyamoya (disappearance of the posterior cerebral artery, and narrowing of individual moyamoya vessels)
Stage V	Reduction of the moyamoya (disappearance of all the main cerebral arteries arising from the internal carotid arterial system, further minimization of the moyamoya vessels, and an increase in the collateral pathways from the external carotid arterial system)
Stage VI	Disappearance of the moyamoya (disappearance of the moyamoya vessels, with cerebral blood flow derived only from the external carotid artery and the vertebral-basilar arterial system)

Table 2 Classification and scoring based on the MRA findings

1) Internal carotid artery	
Normal	0
Stenosis of C1	1
Discontinuity of the C1 signal	2
Invisible	3
2) Middle cerebral artery	
Normal	0
Stenosis of M1	1
Discontinuity of the M1 signal	2
Invisible	3
3) Anterior cerebral artery	
Normal A2 and its distal	0
A2 and its distal signal decrease	1
Invisible	2
4) Posterior cerebral artery	
Normal P2 and its distal	0
P2 and its distal signal decrease	1
Invisible	2

A total score of 1) to 4). Calculate individually for the right and left sides.

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

MRA is effective for assessing the effects of surgical intervention and observing the angiographic changes after treatment (III)[8]. MRI perfusion imaging is also a useful and simple tool for cerebral blood flow evaluation (III)[9].

Evaluation of the cerebral hemodynamics using PET has been

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2. Cerebral Blood Flow SPECT and PET, etc.

1) Recommendation

Evaluation of the cerebral hemodynamics by SPECT and PET is useful for diagnosis and assessment of the severity of cerebral ischemia in patients with ischemic-type moyamoya disease (B).

2) Explanation

1. Clinical significance of the examinations

Cerebral blood flow (CBF)-SPECT and PET have been applied for evaluating the cerebral hemodynamics in patients with moyamoya disease. Assessment of the hemodynamic severity of cerebral ischemia using these diagnostic tools is clinically meaningful for determining the indications of cerebral revascularization and assessment of the therapeutic effects and prognosis, mainly in patients with moyamoya disease.

2. Cerebral hemodynamics in patients with moyamoya disease

reported to reveal hemodynamically-induced cerebral ischemia and typical misery perfusion in both pediatric and adult patients with moyamoya disease[1-3] (III). This clinicopathological condition is characterized by cerebral ischemia, which induces a series of compensatory responses to maintain the cerebral metabolic rate of oxygen ($CMRO_2$), including increase of the oxygen extraction fraction (OEF) (decrease of the cerebral metabolic reserve), because cerebral blood flow (CBF) cannot be maintained by the cerebral vasodilatory response alone (increase of cerebral blood volume [CBV], decrease of cerebravascular reserve) owing to the marked decrease in the cerebral perfusion pressure (CPP). In regard to CBF-SPECT, with the development of the CBF tracers (^{123}I-IMP, ^{99m}Tc- HMPAO and ^{99m}Tc-ECD) and advances in the quantitative analysis procedures since the mid-1990ʻs, both the CBF at rest and the CBF under acetazolamide-activation can be measured quantitatively; these advances in the techniques of SPECT have also enabled assessment of the hemodynamic severity of cerebral ischemia in patients with moyamoya disease[4] (III). In atherothrombotic stroke, Stage 2 hemodynamic cerebral ischemia, defined as ≦80% of the normal resting CBF and
≦10% of cerebrovascular reserve [(CBF under acetazolamide- activation / resting CBF -1) x 100%] as measured by quantitative SPECT is considered to be equivalent to the misery
perfusion demonstrated by PET. Severity assessment using the
same index has also been found to be useful in moyamoya disease patients, but no direct comparisons of the indices obtained using the two examinations have been made. It should be remembered that acetazolamide-activated SPECT should be performed carefully in pediatric patients with moyamoya disease assumed to have severe ischemia, because cerebral ischemia may deteriorate during the examination.

3. Cerebral hemodynamics and outcome

A high recurrence rate in patients with misery perfusion demonstrated by PET, or Stage 2 hemodynamic cerebral ischemia demonstrated by CBF-SPECT after a cerebral ischemic attack, has already been identified among patients with atherothrombotic stroke. For pediatric patients with moyamoya disease, a high recurrence rate of cerebral ischemic attacks has also been reported when the cerebrovascular reserve is markedly decreased[5] (IIb). In pediatric patients, the outcome is poor in the group showing inadequate improvement of the cerebrovascular reserve after revascularization, and a high probability of residual neurological deficit and recurrent ischemic attacks during the course have been reported[6] (IIa).

4. Indications of cerebral revascularization based on evaluation of the cerebral hemodynamics

In general, cerebral revascularization (EC-IC Bypass) is
indicated in patients with misery perfusion (on PET) or Stage 2 hemodynamic cerebral ischemia (on CBF- SPECT), as it can be expected to improve the CPP. For moyamoya disease, because the clinical condition of cerebral ischemia progresses in not only in children but also in adults[7] (IIa), cerebral revascularization is considered when CBF-SPECT demonstrates decreased cerebrovascular reserve in patients with moyamoya disease manifesting as cerebral ischemia[4] (III). Nonetheless, cerebral revascularization can be delayed until the development of ischemic symptoms in pediatric patients with

only unilateral symptoms, as long as the cerebral ischemia on the asymptomatic side is not severe[8] (III). In contrast, even if the cerebrovascular reserve is not decreased, cerebral revascularization has been performed for preventing rebleeding in patients with moyamoya disease manifesting as cerebral hemorrhage. However, there are practically no studies that can be used as evidence. Currently, an investigation of the cerebral hemodynamics is ongoing in the JAM trial in adult patients with moyamoya disease manifesting as cerebral hemorrhage in Japan[9] (III).

5. Cerebral homodynamics after cerebral revascularization

Long-term improvement of the cerebral chemodynamics after cerebral revascularization has been commonly reported, however, the number of reports on the improved postoperative outcome is limited[6] (IIb). A hyperperfusion phenomenon, with transient deterioration of the neurological symptoms, has been reported to be seen sometimes immediately after cerebral revascularization in adult patients with moyamoya disease[10] (III).

6. Cerebral angiographic findings and cerebral hemodynamics

Evaluation of the cerebral angiographic findings and cerebral hemodynamics in adult patients with moyamoya disease manifesting as cerebral ischemia has revealed that cerebral ischemia is more severe in patients with a marked increase over a wide extent of basal moyamoya vessels than in those with less pronounced formation of moyamoya vessels; thus, the degree of development of moyamoya vessels as visualized on cerebral angiograms may well be an index for assessing the severity of cerebral ischemia[11] (III).

7. Re-build-up phenomenon on electroencephalogram and cerebral hemodynamics

Electroencephalography performed in pediatric patients with moyamoya disease manifesting as cerebral ischemia has revealed the characteristic finding of the re-build-up phenomenon, assumed to be associated with a delay in recovery of the cortical CBF after hyperventilation loading[12]. Examination by CBF-SPECT has revealed a marked decrease in the cerebrovascular reserve in the region showing the re-build-up phenomenon and also evident improvement of the cerebral hemodynamics in the region where the re-build-up phenomenon disappeared after cerebral revascularization[13] (III).

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CHAPTER VII. TREATMENT

1. Surgical Treatment

1) Recommendations

Surgical revascularization is effective for moyamoya disease manifesting with cerebral ischemic symptoms (B).

2) Explanation

1. Candidates for surgery

Surgical revascularization for moyamoya disease patients with cerebral ischemic attacks has been reported to reduce the frequency of transient ischemic attacks and the risk of cerebral infarction, and improve the postoperative ADL and long-term prognosis of higher brain functions[1-8] (IIb). Improvement of the cerebral hempdynamics and metabolism has been reported following revascularization surgery in patients with hemodynamic compromise, noted on preoperative evaluation, by SPECT or PET[1,8,9] (IIb).

2. Surgical procedures

In regard to the revascularization procedures for moyamoya disease, direct revascularizations such as superficial temporal artery–middle cerebral artery (STA-MCA) anastomosis, and indirect pial synangiosis such as encephalo-myo-synangiosis (EMS), encephalo-arterio-synangiosis (EAS), encephalo-duro-synangiosis (EDS) and multiple burr hole surgery have been employed. Both direct and indirect revascularizations alone or a combination of the two types of procedures have been reported to improve cerebral hemodynamics, ameliorating the severity/frequency of ischemic attacks, reducing the risk of cerebral infarction, and improving the postoperative ADL and long-term prognosis of the higher brain functions in the patients[1-10] (IIb). The effect of indirect procedure alone is not very significant in adult patients, but direct revascularization is often effective[11]. In pediatric patients, surgical revascularization, regardless of whether direct or indirect revascularization has been performed, has been reported to improve the prognosis[12,13] (IIb).

3. Perioperative management

During the perioperative period, the blood pressure should be maintained, normocapnea should be ensured, and adequate body fluid balance should be maintained, while paying attention to ischemic complications, including on the non-surgical side[14] (III). When neurological symptoms may appear during the acute phase after revascularization, it has been reported to be useful to bear in mind clinical conditions such as cerebral hyperperfusion syndrome while evaluating the cerebral hemodynamics [15] (III).

4. Postoperative evaluation

Postoperative assessment of improvement of the cerebral blood flow and of the cerebrovascular reserve capacity by PET and/or SPECT is considered to be useful for evaluating the effect of revascularization[1,8,9]. Not only cerebral angiography, but also MRA has been reported to be useful for evaluation of development of the bypass flow [16,17] (III).

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2. Medical Treatment

1) Recommendations

Oral administration of antiplatelet agents is recommended as a medical treatment for moyamoya disease, however, adequate scientific evidence for this recommendation is still lacking (C1).

2) Explanation

The medical treatment of moyamoya disease is roughly classified into treatment for the acute phase of stroke, treatment for preventing recurrence in the chronic phase of stroke, and treatment of asymptomatic moyamoya disease.

1. Acute phase

Intravenous tPA (alteplase) therapy is contraindicated in moyamoya disease manifesting as cerebral ischemia ("Guidelines for Proper Treatment with Intravenous tPA (Alteplase) Therapy" by the Japan Stroke Society)[1]. In adult patients with moyamoya disease manifesting as cerebral infarction, the use of edaravone, a cerebroprotective agent, and of antithrombotic drugs such as ozagrel, argatroban, aspirin and heparin has been recommended, as specified for the treatment of atherothrombotic cerebral infarction[2]. Although there is only insufficient evidence, these drugs are considered to be effective in patients with cerebral infarction caused by moyamoya disease (III). For patients with large infarcts causing cerebral edema and intracranial hypertension, glycerol is reportedly effective (III). Furthermore supportive treatment, such as antipyretics for fever, anticonvulsants for convulsions, proper control of blood sugar, oxygen supplementation for maintenance of the arterial oxygen saturation, and prophylactic administration of antiulcer agents for severe case, is considered to be important in patients in the acute phase of cerebral infarction in general (III). When mechanical ventilatory support is necessary, the partial pressure of carbon dioxide in the arterial blood should be kept above 40 mmHg. In regard to blood pressure control, as in the treatment of other cerebral infarction, the blood pressure should not be lowered during the acute phase, as a rule (III).

Treatment of moyamoya disease manifesting as cerebral infarction in children has rarely been reported. Antiplatelet therapy with aspirin (1 to 5 mg/kg) has been reported to be effective (III). Similar to the case in adult patients with moyamoya disease manifesting as ischemia, administration of edaravone, a cerebroprotective agent, and of ozagrel and argatroban, antithrombotic drugs, can be considered for pediatric patients. Anticonvulsants should be used for the treatment of convulsions. The use of aspirin can be considered while keeping in mind that it may increase the risk of development of Reye"s syndrome in pediatric patients.

For adult patients with moyamoya disease manifesting as bleeding, antihypertensive therapy is likely to be effective, in

accordance with the treatment of cerebral hemorrhage, when the systolic blood pressure is $^{24}_{12}$180 mmHg, diastolic blood pressure is $^{24}_{12}$105 mmHg, or the mean blood pressure is $^{24}_{12}$130 mmHg. Any antiplatelets in use should be discontinued, any anticoagulant therapy should be immediately stopped, and the use of vitamin K and blood products (fresh frozen plasma and factor IX complex) should be considered (III).

2. Prevention of recurrence in the chronic phase

The indications of surgical treatment for the prevention of recurrence should be examined first in patients with moyamoya disease manifesting with a cerebral ischemic attack. Medically, oral administration of aspirin is recommended, but attention is required, because long-term aspirin treatment may convert the disease type from ischemic to the hemorrhagic type (III). Whether or not a regular follow-up for the development of microbleeds using MRI T2* might be effective for the prevention of bleeding is a topic that needs to be examined in the future[5]. When patients cannot tolerate aspirin, or aspirin does not appear to be beneficial for the ischemic attack, use of clopidogrel, a thienopyridine drug, is recommended. Clopidogrel also has good tolerability and safety profiles in children[6]. However, long-term combination of aspirin and clopidogrel is believed to increase the risk of bleeding complications. Especially, in patients with severe moyamoya disease showing marked cerebral atrophy, or the moyamoya vessels with weakened walls are present in abundance, combined use of two or more antiplatelet agents has been reported to elevate the risk of cerebral hemorrhage (III)[6].

Risk factors for stroke should be managed in accordance with that in general: antihypertensive therapy for hypertension, lipid-lowering therapy for dyslipidemia, adequate blood sugar control for diabetes mellitus, and smoking cessation, and weight reduction advice for obese people. In terms of lifestyle guidance, hyperventilation often induces the symptoms of moyamoya disease; therefore, pediatric patients should avoid hot meals (noodles, soup, etc.), strenuous exercise, playing wind instruments such as a flute, and blowing balloons (III). In infants, crying also induces symptoms, therefore crying should be avoided.

3. Medical management of asymptomatic moyamoya disease

Even asymptomatic patients diagnosed as having moyamoya disease are at an elevated risk of developing cerebrovascular events during follow-up, regardless of whether the disease is the ischemic type or the hemorrhagic type[7]. Unlike in quasi- moyamoya disease with underlying disease (e.g. atherosclerosis and angiitis), there are no effective procedures for preventing vascular lesions in patients with moyamoya disease of unknown cause; therefore, surgical treatment for the prevention of future stroke can be considered even in asymptomatic patients. Medically, the management of risk factors and lifestyle guidance should be implemented in accordance with the prevention of recurrence in the chronic phase (III). In adults, the use of antiplatelet agents should not be considered for asymptomatic patients, because nearly a half of the patients with moyamoya disease manifest bleeding.

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3. Treatment for Patients with Moyamoya Disease Manifested as Hemorrhage

1) Recommendations

While revascularization can be considered for patients with hemorrhagic-type moyamoya disease, adequate scientific evidence is still lacking (C1).

2) Explanation

Intracranial bleeding in patients with moyamoya disease is the most significant factor worsening the survival and functional prognosis of the patients[1] (III). Hemorrhage is assumed to be caused by collapse of the dilated vessels of the collateral circulation (moyamoya vessels), due to hemodynamic loading and rupture of the peripheral aneurysms often formed on moyamoya vessels. The rebleeding rate in patients with hemorrhagic-type moyamoya disease is reportedly 7.09%/year[2] (III).

No treatment policy for the prevention of rebleeding has yet been established. In cerebral angiography performed after direct revascularization in patients with moyamoya disease, reduction in the number of moyamoya vessels and/or disappearance of the peripheral aneurysm has been reported[3,4] (III). Based on the assumption that the hemodynamic loading on these collateral vessels is reduced, it has been hypothesized that direct revascularization may prevent or reduce the incidence of rebleeding. In patients with ischemic-type moyamoya disease undergoing direct revascularization, the frequency of conversion to the hemorrhagic type of the disease on long-term follow-up has been reported to be reduced as compared with that in patients treated conservatively[5] (III).

It has been reported that the rebleeding rate is significantly lower in patients with hemorrhagic-type moyamoya disease undergoing revascularization procedures as compared with that in patients receiving only conservative medical treatment[6] (III); there are other reports suggesting that the frequency of rebleeding and ischemic attacks is significantly decreased after direct revascularization in patients with hemorrhagic-type moyamoya disease[7,8] (III). On the other hand, there are also a number of reports denying the beneficial effect of revascularization on the prevention of rebleeding[9-11] (III). It has been reported that the effect of indirect revascularization on hemorrhagic-type moyamoya disease is inferior to that on the ischemic type of the disease, and neovascularization or a decrease in the number of moyamoya vessels cannot be achieved in many cases[12] (III). However, a beneficial effect of revascularization on the prevention of cerebrovascular events, including ischemic attacks, has been reported in patients with hemorrhagic-type moyamoya disease [7]; thus, it appears that revascularization may be more effective for hemorrhagic-type moyamoya disease patients with ischemic attacks.

A randomized, controlled trial (RCT) to demonstrate the effect of direct revascularization on the prevention of rebleeding in patients with moyamoya disease was initiated in Japan in 2001, and is currently ongoing (Japanese Adult Moyamoya (JAM) Trial)[13] (Ib). The JAM Trial is a multicenter study in which patients with hemorrhagic-type moyamoya disease are randomly assigned to a group undergoing direct bilateral revascularization of the cerebral hemispheres or a group administered conservative medical treatment only, and then the patients of both groups are followed up for at least 5 years.

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CHAPTER VIII PROGNOSIS (NATURAL HISTORY)

1. Pediatric Moyamoya Disease

Episodes of transient cerebral ischemia occur most frequently a few years after the onset of moyamoya disease, thereafter the frequency usually decreases. However, the frequency increases with the passage of time after the disease onset in patients with intellectual disturbance and dysfunction, and the severity also deteriorates[1)]. In younger infants, cerebral infarction, especially cortical infarction, occurs often, and the presence/absence of cerebral infarction is assumed to be the most important factor associated with the functional prognosis[2-4)]. In children, the disease stage progresses in many patients, but the speed of progression becomes gradual during puberty[5,6)]. It has been reported that during long-term follow-up, unilateral lesions often change to bilateral lesions, and that TIA arising from the cerebral hemispheres occurs in 65% of patients who were originally asymptomatic[7)]. When the disease persists until adulthood, the ADL is favorable in only a small number of patients[8)], and intracranial hemorrhage may result in death in a few patients[5,9)].

There are no reported RCTs conducted to examine the effect of cerebral revascularization. However, following cerebral revascularization, it is assumed that the TIAs would decrease in frequency or disappear altogether, that recurrent cerebral infarction would be quite rare regardless of the surgical procedure employed, and that the functional prognosis would be better as compared with that in untreated patients[4,10-19)]. Cerebral revascularization has been shown to result in a reduced frequency/severity of headache, but it has also been reported that even after surgery, irrespective of the improvement of the cerebral circulatory dynamics, headache may persist or even appear anew[20,21)]. Higher brain functions are also an important factor influencing the prognosis, and a decrease of the IQ often becomes evident 5 years or more after the disease onset[22)]. Cerebral revascularization is believed to improve the intellectual prognosis[23)].

2. Adult Moyamoya Disease

A higher recurrence rate of cerebrovascular events and a poorer prognosis have been reported in adult patients with untreated moyamoya disease than in those undergoing surgical treatment, regardless of the disease type manifested at the initial attack[24, 25)]. As for the case of pediatric patients, cerebral revascularization should be considered.

In recent years, disease progression has been found to be more frequent than previously assumed[26-29)]. Irrespective of the symptomatic/asymptomatic status of the patients or of a definitive/probable diagnosis, disease progression has been reported to occur in approximately 20% of the cases in the non-surgically treated hemisphere, and TIA/cerebral infarction or intracranial hemorrhage has been reported to occur in about half of the cases. Disease progression is known to be more likely to occur in women[30)]. With regard to the complications during pregnancy and delivery in women with moyamoya disease, serious stroke events, such as intracranial hemorrhage, have been reported to occur occasionally. Evidence-based management policies have not yet been established. Rigorous management during pregnancy, delivery and puerperium in an environment of active collaboration between the obstetrician and neurosurgeon is recommended[31,32)].

1) Adult ischemic-type moyamoya disease

As for the case of children with the disease, there are no RCTs conducted to examine the efficacy of cerebral revascularization in adult patients with moyamoya disease. A marked decrease of the frequency of TIA and cerebral infarction has been reported after cerebral revascularization. Nonetheless, intracranial hemorrhage and cerebral infarction attributable to disease progression in the non-surgically treated hemisphere may occur in few patients during the follow-up period; therefore, long-term follow-up is believed to be important after surgery for ensuring that a good prognosis is maintained[17,33-36)].

2) Adult hemorrhagic-type moyamoya disease

The estimated mortality of patients presenting with intracranial hemorrhage at the initial attack ranges from 6.8 to 20%. Rebleeding worsens the functional prognosis and increases the mortality[37,38)]. Rebleeding may occur at the same site as that in the initial episode, or at a different site[39)].

It has been reported that following conservative treatment, rebleeding may occur 2 to 20 years after the initial bleeding in 30 to 65% of the patients, and that the incidence tends to increase with increasing duration of the follow-up period[37,38,40-42)]. The risk of rebleeding is reportedly higher in patients with abnormal dilation of the anterior choroidal artery or posterior communicating artery branches[42,43)]. The disappearance of aneurysms formed in moyamoya vessels after cerebral revascularization has also been reported[44)].

The effect of revascularization on the prevention of rebleeding is unknown at present. However, long-term follow-up is considered to be essential, regardless of whether or not a patient has been treated by cerebral revascularization.

3. Asymptomatic Moyamoya Disease

In recent years, with the advances and spread of non-invasive diagnostic imaging, the number of patients diagnosed as having moyamoya disease even before the onset of symptoms has been growing. A recent follow-up investigation by the Research Committee revealed that the disease progresses with age, and that as many as 20% and 40% of patients with cerebral infarction and cerebral circulatory disturbance, respectively, are at a high risk for cerebral ischemia[45)].

The prognosis of asymptomatic moyamoya disease remains unknown for the most part. According to a previous report, 4 out of 33 patients developed TIA, and 2 patients died of intracranial hemorrhage[46)], and 1 of 10 patients developed cerebral infarction with the progression of the disease[47)]. In a recent follow-up investigation, the disease progressed in 5 of 34 untreated patients, and the risks of cerebral infarction and intracranial hemorrhage were reported to be 3.2%/year. While

cerebral infarction occurred more frequently in patients found to have cerebral ischemia on medical examination, no cerebrovascular events reportedly occurred in the 6 patients who underwent cerebral revascularization[45]. Therefore, patients with asymptomatic moyamoya disease are also considered to be potentially at risk for cerebrovascular events. When the disease is conservatively followed up, careful long-term observation of the course using MRI/MRA is considered to be necessary.

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Classification of evidence levels and recommendation grades in the Guidelines.

Table 1 Classification of evidence levels in the Guidelines

Evidence level	Contents
Ia	A meta-analysis of RCTs (The results of RCTs are practically consistent.)
Ib	RCT
IIa	Well-designed controlled study (non-randomized)
IIb	Well-designed quasi-experimental study
III	Well-designed non-experimental, descriptive study (comparison/ correlation/ case study)
IV	Report/comments/experience of specialists

This classification is according to that adopted in the "2004 Guidelines for Stroke Treatment" by the Japan Stroke Society.

Table 2 Classification of recommendation grades in the Guidelines

Recommendation grade	Contents
A	Strongly recommended
B	Recommended
C1	Can be considered, but adequate scientific rationale lacking
C2	Not recommendable because of absence of scientific rationale
D	Not recommended

Precautions for the use of the Guidelines

(1) The clinical condition needs to be assessed in individual patients, and the Guidelines are not uniformly applicable to all individual patients. Therefore, the judgment of the treating physician who most accurately understands his/her patient"s clinical condition should be afforded priority in the management of patients with moyamoya disease.

(2) The Guidelines should not be referred to without careful consideration, used as data for evaluation of medical examinations, or for medical accidents or lawsuits. Attention should be paid to the fact that the Guidelines include drugs not approved or therapies not authorized in Japan and drugs used for purposes other than the original intent.

(3) The number of patients is small and the cause of moyamoya disease is still unknown. Therefore, there are many aspects of the disease that still remain unresolved and for which adequate amount of evidence has not yet been collected. Therefore, it must be borne in mind while using the Guidelines that there may be many inaccuracies and that the contents may not always necessarily be up to date or the best for the time.

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『無症候性もやもや病の予後と治療法の確立
をめざした多施設共同研究』
Asymptomatic Moyamoya Registry (AMORE)
プロトコール

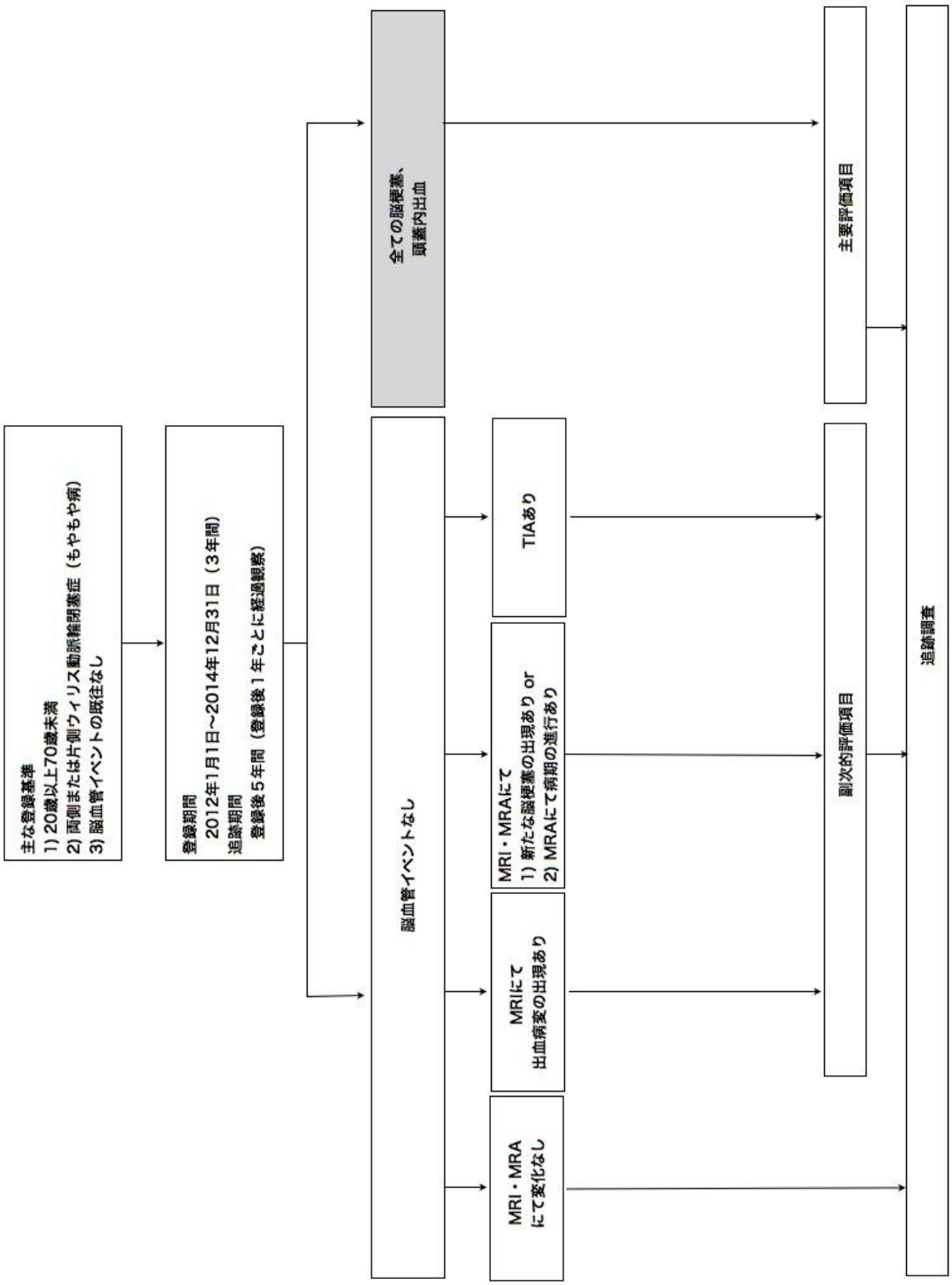
厚生科学研究費特定疾患対策研究事業

～ウィリス動脈輪閉塞症の病因・病態に関する研究～

Ver 2.1.0　2011年10月26日

0. 概 要

0.1. フローチャート



1.2　. 目　的

無症候性ウィリス動脈輪閉塞症（もやもや病）の疫学・病態・予後を明らかとする。

1.3　. 登録基準

新たにウィリス動脈輪閉塞症と診断された 20～70 歳の患者のうち、それまでに一 過性脳虚血発作、脳梗塞、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症例。

0.4. 目標登録症例数

200 症例

0.5. 研究期間

登録期間：3 年、観察期間：5 年（合計 8 年）

0.6. 研究デザイン

多施設共同観察研究

0.7. 連絡先

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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。