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Kumamoto University
Analysis of cerebral artery stenosis in moyamoya disease
（もやもや病における脳血管狭窄の分析）

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Degree Thesis

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2012年3月
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1. Summary

To obtain information on affected vessels in moyamoya disease (MMD) we have analyzed the vascular morphological characteristics of MMD using three-dimensional (3D) constructive interference in steady-state (CISS) magnetic resonance imaging (MRI).

The population of this 3D-CISS MRI studies consisted of 51 patients with MMD; 16 patients with atherosclerotic middle cerebral artery (MCA) stenosis or occlusion; 42 MRI control patients; and 28 control digital subtraction angiography (DSA) patients. We measured the outer diameters of the terminal portion of the internal carotid artery (ICA), the proximal portion of the MCA (M1 portion). We evaluated the inner diameter as the relative value (%) obtained from magnified DSA images and analyzed these data.

The outer diameters of the ICA and M1 portion were significantly smaller in the MMD group than in the other 2 groups, while the M1 outer diameter of the atherosclerosis group was not significantly different compared to the control (ICA: MMD, 2.61 ± 0.46 mm vs. control, 4.04 ± 0.50mm and M1: MMD, 1.92 ± 0.43mm vs. control, 3.34 ± 0.54mm vs. atherosclerosis, 3.45 ± 0.56mm). Furthermore, in MMD the outer diameter was unrelated to the progression of luminal stenosis grade estimated by DSA.

This is the first report that the outer diameters of both the ICA and M1 decrease in MMD patients. Our findings suggest that the vascular constrictive changes of the affected arteries are the important phenomenon reflecting MMD pathology.
2. Lists of published papers

   Outer-diameter narrowing of the internal carotid and middle cerebral arteries in moyamoya disease detected on 3D constructive interference in steady-state MR image: is arterial constrictive remodeling a major pathogenesis?
   *Acta Neurochir.* 2012;154:2151-7

   Cerebral blood flow and metabolism of hyperperfusion after cerebral revascularization in patients with moyamoya disease.
   *J Cereb Blood Flow Metab* 2012;32:2066-75
3. Acknowledgements

I gratefully acknowledge all of excellent advisers; Dr. Motohiro Morioka (Department of Neurosurgery, Kurume University), Dr. Yuki Ohmori, Dr. Takayuki Kawano, Dr. Yutaka Kai (Department of Neurosurgery, Kumamoto University) and Dr. Toshinori Hirai (Department of Diagnostic Radiology), for the study design and the manuscript preparation. This study has been conducted under the guidance of Professor and Chairman Jun-ichi Kuratsu at Department of Neurosurgery, Kumamoto University Graduate School of Medical Sciences.

This work was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Sports, Science and Culture of Japan.
### 3. Abbreviation and Acronyms

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<th>Description</th>
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<tr>
<td>3D</td>
<td>3-dimensional</td>
</tr>
<tr>
<td>ACA</td>
<td>anterior cerebral artery atherosclerosis</td>
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<tr>
<td>ANOVA</td>
<td>analysis of Variance</td>
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<tr>
<td>BA</td>
<td>basilar artery</td>
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<tr>
<td>CBF</td>
<td>cerebral blood flow</td>
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<td>CBV</td>
<td>cerebral blood volume</td>
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<td>CISS</td>
<td>constructive interference in steady-state</td>
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<td>CMRO$_2$</td>
<td>cerebral metabolic rate of oxygen</td>
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<td>CPP</td>
<td>cerebral perfusion pressure</td>
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<td>DSA</td>
<td>digital subtraction angiography</td>
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<td>ICA</td>
<td>internal carotid artery</td>
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<td>M1</td>
<td>horizontal portion of the middle cerebral artery</td>
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<td>MCA</td>
<td>middle cerebral artery</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>MRA</td>
<td>magnetic resonance angiography</td>
</tr>
<tr>
<td>MMD</td>
<td>moyamoya disease</td>
</tr>
<tr>
<td>NS</td>
<td>not significant</td>
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<tr>
<td>OEF</td>
<td>oxygen extraction fraction</td>
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<tr>
<td>PET</td>
<td>positron emission tomography</td>
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<td>SD</td>
<td>standard deviation</td>
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<tr>
<td>SPECT</td>
<td>single-photon emission computed tomography</td>
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<tr>
<td>STA</td>
<td>superficial temporal artery</td>
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<td>TIA</td>
<td>transient ischemic attack</td>
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5. Background and purpose

5-1 Moyamoya disease

I Concepts of the Disease

The characteristics of moyamoya disease (MMD) (spontaneous occlusion of the circle of Willis, cerebrovascular “moyamoya” disease) on cerebral angiography were reported for the first time in 1957 (Takeuchi K and Shimizu K. 1957), and the concept of MMD as a separate disease entity was established in the 1960s. Pathologically, moyamoya disease is characterized by chronic progressive stenosis of the terminal portion of the bilateral internal carotid arteries, which leads to the formation of an abnormal vascular network composed of collateral pathways at the base of the brain (‘moyamoya’ is the Japanese terms for a “puff of smoke”, which has been used to describe the appearance of these collateral vessels on cerebral angiograms (Suzuki J and Takaku A. 1969) (Fig. 1). Eventually, with bilateral internal carotid artery occlusion, the moyamoya vessels at the base of the brain derived from the internal carotid artery disappear, and the entire brain is perfused by the external carotid artery system and the vertebrobasilar artery system. This disease is in included in the list of disease for Research on Measures for Intractable Diseases and the Specified Disease Treatment Research Program specified by the Ministry of Health, Labour and Welfare. Currently, the diagnosis criteria for moyamoya disease (Spontaneous occlusion of the circle of Willis) laid down by the research committee (Research committee on the pathology and treatment of spontaneous occlusion of the circle of Willis. 1998).
Fig. 1
(A) Normal cerebral angiography. It shows internal cerebral artery (ICA) normally supplies to both ACA and MCA
(B) Schema and cerebral angiography of moyamoya disease. It is characterized by stenosis or occlusion at the terminal portions of the ICA or the proximal areas of the anterior or middle cerebral arteries and abnormal vascular networks in the arterial territories near the occlusive or stenotic lesions
(C) Schema and cerebral angiography show MCA stenosis due to atherosclerosis.
II Epidemiology

Moyamaoya disease is a disease that occurs frequently in Asian countries, including Japan, but is rare in Western countries. Epidemiological data reported from Japan are extremely valuable worldwide. MMD affects 3.16 people per 100,000 persons, and occurs at an incidence of 0.35 people per 100,000 populations. The male:female ratio reported from various studies is nearly consistent, 1:1.8 to 1.9. The disease is more common in women. In addition, a positive family history has been reported in about 10% of the patients. The age of onset showed a trend: a bimodal peak consisting of a major peak in the first decade of life and a moderate peak in the late 20s to 30s (Wakai et al.1994). The various disease types by which the initial attack can manifest are presented in detail in chapter: symptoms.
III Pathology/Etiology

1. Pathology

The main finding at autopsy is stenosis or occlusion of the terminal portion of the internal carotid arteries. Moyamoya vessels are assumed to represent collateral circulation which has developed to compensate for the cerebral ischemia occurring due to stenosis. Degeneration of the smooth muscle cells in the media and resultant death of the vascular smooth muscle cells cause thinning of the media. The waviness and duplication of the internal elastic lamina, accumulation of the necrotic cell components in the interstitial, and proliferation of the vascular smooth muscle cells induce thickening of the intimal and narrowing of the intravascular lumen. These are the process assumed to be involved in the formation of the occlusive lesion (Oka et al. 1981). These changes noted in the terminal portion of the internal carotid arteries suggest the possibility of similar occurrence in the systemic arteries (Weber C et al. 2001).

2. Genetic factors

For familial moyamoya disease, gene loci have been identified in 17q25 (Yamauchi et al. 2000) in a chromosomal search. In families with strong genetic factors, in which affected people are identified in 3 or more generations, the disease assumes an autosomal dominant inheritance pattern, and a significant linkage to 17q25.3 has been noted in these families (Mineharu Y et al. 2008). Recently, RNF213 is identified susceptibility gene for MMD (Kamada F et al. 2011) and its possible role in vascular development (Liu W et al. 2011).
IV Symptoms

1. Disease type manifested at the initial attack

MMD may occur at any age from childhood to adulthood. In general, the initial manifestation is cerebral ischemic symptoms in children and intracranial hemorrhage symptoms in addition to ischemic symptoms in adults. The Research Committee on Moyamoya Disease classified the initial attacks into 6 types in 1979: “hemorrhage-type”, “epileptic-type”, “infarction-type”, “transient ischemic attack (TIA)-type”, “frequent TIA-type” (twice or more often per month), and “other”. Subsequently, the “asymptomatic-type” was added, and in 2003 “headache-type” was also added.

2. Characteristics of symptoms according to the age and disease type

Symptoms vary according to the age and disease type. In children, the disease often manifests initially with cerebral ischemic symptoms, particularly, after hyperventilation caused by strenuous exercise, crying, harmonica playing, and eating a hot meal. Symptoms such as cataplexy (quadriplegia, hemiplegia, and monoplegia), sensory disturbance, consciousness disturbance, seizure, and headache occur in a paroxysmal and recurrent manner. The symptoms always appear on the same side in many patients, but occasionally, the affected side interchanges between the right and left sides. In pediatric patients, particularly those aged less than 5 years old, intracranial bleeding rarely occurs, unlike in adult patients. In adult patients, especially those aged 25 years or older, moyamoya disease frequently manifests with sudden-onset intracranial hemorrhage (intraventricular, subarachnoid space, or intracerebral hemorrhage), causing symptoms such as consciousness disturbance, headache, muscle weakness, and speech disorder, according to the site of hemorrhage. The patients are at a high
risk of rebleeding, and approximately a half of the patients die as a result of bleeding. In addition to these symptoms, MMD may also manifest as cerebral ischemia attacks in adult patients. In such patients, age-related vascular changes are also present. This may cause cerebral infarction, resulting in permanent impairment in many cases. With the recent widespread availability of MRI, an increasing number of patients with only headache or even entirely asymptomatic patients are detected to have moyamoya disease.

V Diagnosis

1. Diagnostic Criteria

(1) Cerebral angiography is considered essential for the diagnosis, and most show at least the following findings:

(i) Stenosis or occlusion of the terminal portion of the intracranial internal carotid artery or the anterior and/or the middle cerebral artery.

(ii) Abnormal vascular networks in the vicinity of the occlusive or stenotic lesions in the arterial phase

(2) However, when magnetic resonance imaging (MRI) and magnetic resonance angiographic (MRA) findings meet all of the following criteria (Fig. 2), cerebral angiography can be omitted.

(i) MRA shows stenosis or occlusion of the terminal portion of the intracranial internal carotid artery of proximal portions of the anterior and/or the middle cerebral artery.

(ii) MRA shows abnormal vascular networks in the basal ganglia. Note: when 2 or more visible flow voids are present in the basal ganglia on MRI, at least
unilaterally, they can be deemed as representing an abnormal vascular
network.

(iii) Bilaterality of findings (i) and (ii).

(3) Moyamoya disease is an illness of unknown etiology. The differential diagnosis of
this disease includes similar cerebrovascular lesions associated with the following
underlying disease, which should, therefore, be excluded: (i) atherosclerosis, (ii)
autoimmune disease, (iii) meningitis, (iv) brain tumor, (v) Down’s syndrome, (vi) von
Recklinghausen’s disease, (vii) head injury, (viii) cerebrovascular lesions after head
irrigation and (ix) others.

(4) Pathological findings that can be used as reference for the diagnosis

(i) Thicking of the arterial intima, mainly in the terminal portion of the internal
carotid arteries, and narrowing or blockage of the lumen caused by this change,
usually bilateral. Occasionally, lipid deposits are also present in the thickened
intima.

(ii) Arteries such as the anterior, middle, and posterior cerebral arteries forming the
circle of Willis occasionally show varying degrees of stenosis or occlusion
associated with fibrocellular thickening of the intima, waviness of the internal
elastic lamina, and thinning of the media.

(iii) Numerous small vascular channels (perforating and anatomic branches) can
be seen around the circle of Willis.

(iv) Pia mater may also show reticular conglomerates of small vessels.
2. Diagnostic Assessment

Moyamoya disease should be classified as definitive or probable based on the above-mentioned items (1) to (4). When autopsy is performed in the absence of cerebral angiography, the condition should be diagnosed based on the criteria in item (4). **Definitive moyamoya disease:** All criteria listed in (1) or (2) and in (3) should be met. In children, however, the criteria in item (1) or (2) (i) and (ii) on one side, and visible stenosis around the terminal portion of the internal carotid arteries on the other side are sufficient for a definitive diagnosis. **Probable moyamoya disease:** All criteria are fulfilled except item (1) (iii) and/or (2) (iii) among the criteria of (1) or (2) and (3).

**Fig. 2  Typical findings of moyamoya disease seen with MRI and CT**

(A) T2-weighted MRI shows the disappearance of the flow void signal of the horizontal portion (M1) of the middle cerebral artery (left panel, arrow) and many small flow void signals in the basal cistern (right panel).  (B) T1-weighted MRI shows the flow voids in the basal ganglia (arrow).  (C) Diffusion-weighted MRI shows acute ischemic damage in the left lobe.  (D) Plane CT scan shows massive intraventricular hematoma associated with intracerebral hematoma.
3. CBF - PET and SPECT

Evaluation of the cerebral hemodynamics by positron emission tomography (PET) and single emission computed tomography (SPECT) (Fig. 3) is useful for diagnosis and assessment of the severity of the cerebral ischemia in patients with ischemic-type moyamoya disease. PET reveals hemodynamically-induced cerebral ischemia and typical misery perfusion in the patients with MMD. The clinicopathological condition is characterized by cerebral ischemia, which induced a series of compensatory responses to maintain the cerebral metabolic rate of oxygen, including increase in the oxygen extraction fraction (decrease in the cerebral metabolic reserve), because CBF cannot be maintained by only the cerebral vasodilatory response (increase in cerebral blood volume, decrease in cerebrovascular reserve) owing to the marked decrease in the cerebral perfusion pressure (Powers WJ. 1991). In regard to CBF-SPECT, 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. For moyamoya disease, because the clinical condition of cerebral ischemia progresses not only in children but also in adult, cerebral revascularization is considered when CBF-SPECT demonstrates decreased cerebrovascular reserve in patients with moyamoya disease manifesting as cerebral ischemia. 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, as investigation of the cerebral hemodynamics is ongoing in the Japanese Adult Moyamoya (JAM) Trial in adult patients with moyamoya disease.
manifesting as cerebral hemorrhage in Japan (Miyamoto S. 2004).

Fig.3

Cerebral angiography (A) and $^{123}$I-IMP SPECT of Moyamoya disease (B)

N-isopropyl-p-$^{123}$I-iodoamphetamine ($^{123}$I-IMP) single photon emission computed tomography (SPECT) shows cerebral hypoperfusion induced by progressive arterial stenosis.

(A)                                   (B)

VI Treatment

1. Surgical Treatment

Surgical revascularization is effective for moyamoya disease manifesting as cerebral ischemic symptoms. In regard to the revascularization procedures for moyamoya disease, direct revascularization such as superficial temporal artery (STA)-middle cerebral artery (MCA) anastomosis, indirect pial synangiosis such as encephalo-myo-synangiosis(EMS), encephalo-duro-arterio-synangiosis, encephalo-arterio-synangiosis (EDAS), encephalo-duro-synangiosis(EDS), and multiple burr hole surgery have been employed (Fig.4). Both direct and indirect
revascularization or a combination of these 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 (Karasawa et al., 1977; Matsushima et al., 1981; Ozgur et al., 2006; Shirane et al., 1997).

Fig. 4
The scheme of the clinical direct and indirect bypass surgery.

2. Medical treatment
The medical of moyamoya disease is roughly classified into treatment for acute phase of stroke, treatment for preventing recurrence in the chronic phase of stroke, and treatment of asymptomatic moyamoya disease. Oral administration of antiplatelet agents is recommended.

3. Hyperperfusion syndrome
Superficial temporal artery (STA)–middle cerebral artery (MCA) anastomosis or various kinds of indirect bypasses are recommended for symptomatic patients based on the
degree of hemodynamic compromise in MMD (Kuroda and Houkin 2008; Takahashi and Miyamoto 2010). Despite favorable long-term outcomes after successful bypass surgery for MMD, recently, cerebral hyperperfusion has received much attention as a possible cause of transient neurological dysfunction after bypass surgery for MMD (Fujimura et al. 2007; Fujimura et al. 2009; Fujimura et al. 2011; Furuya et al. 2004; Kim et al. 2008; Ogasawara et al. 2005). The main neurological deficits corresponding to dysfunctions around the bypass site at the perisylvian area include dysarthria, hand motor dysfunction, and motor or sensory dysphasia. A critical definition of CBF using positron emission tomography (PET), a gold standard, for the diagnosis of hyperperfusion after bypass surgery for MMD remains unestablished. Here we also reported, for the first time in MMD, CBF and oxygen metabolism with pre- and postoperative PET and analyzed the correlation of preoperative PET parameters with development of symptomatic hyperperfusion (Kaku et al. 2012). Symptomatic hyperperfusion in MMD is characterized by temporary increases in CBF more than 100% over preoperative values. Preoperative increases in CBV persisted during hyperperfusion and decreased 3–4 months postoperatively, suggesting the prolonged recovery of high CBV values, despite immediate increases in perfusion pressure after direct bypass, may play a key role in the development of hyperperfusion and the associated clinical symptoms lasting for 1–14 days in our patients. Accordingly, the preoperative decreased CBF/CBV, which was an index of an index of cerebral perfusion pressure (CPP) (Gibbs et al. 1984), increased rapidly within 2–7 days of surgery (Fig. 5&6). In MMD patients, the incidence of symptomatic hyperperfusion after bypass surgery varies considerably from 16.7 to 50.0% (Fujimura et al.; Kaku et al. 2012; Uchino et al. 2012), which is higher than atherosclerotic cases. The incidence is 3.7% (Heros et
We suggested that symptomatic hyperperfusion after bypass surgery is a specific feature of MMD. We clarified the cerebral blood flow and oxygen metabolism of hyperperfusion. As mentioned above, the prolonged recovery of high CBV values may play a key role in the development of hyperperfusion.

Fig. 5
Graphs showing sequential changes in CBF(A), CBV(B), CPP(CBF/CBV, C), CMRO$_2$(D), and OEF(E) at 3 different time points: preoperative (pre), subacute postoperative (2-7D), and chronic postoperative (3-4M). Mean values ± standard deviation are shown.
Fig. 6
A series of PET studies of a MMD patient with symptomatic hyperperfusion.
Left: Preoperative examinations revealed severe hypoperfusion in the right hemisphere with markedly increased CBV and OEF. CBF/CBV was markedly decreased. Middle: Studies obtained on postoperative day 3 demonstrating a marked increase in CBF (white arrow), with persistent increased CBV. Although CMRO$_2$ was slightly increased, OEF markedly decreased. Right: Postoperative examinations obtained 3 months after revascularization. CBF, CMRO$_2$, and OEF were normalized, and CBV and CBF/CBV were improved over the preoperative status. POD, post-operative day
VII Prognosis

1. Child Moyamoya disease

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 (Ishikawa et al. 1997; Karasawa et al. 1992; Miyamoto et al. 1998; Scott RM et al. 2004).

2. Adult moyamoya disease

As for the case of children with disease, there are no RCTs conducted to examine the efficacy of cerebral revascularization in adult patients with moyamoya disease. A marked decrease in the frequency of TIA and cerebral infarction has been reported after cerebral revascularization (Kohno K et al. 1998; Okada Y et al. 1998). On the other hand, 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 (Kobayashi E et al. 2000; Yoshida Y et al. 1999). Rebleeding may occur at the same site as that in the initial episode. 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.
5-2  3D-CISS MR images

Although conventional and digital subtraction angiography (DSA) is the most reliable diagnostic modalities, magnetic resonance imaging (MRI) yields more important information. The classical MR findings of MMD are the loss of flow voids in major arteries around the supraclinoid internal carotid arteries (Hasuo et al. 1998; Yamada et al. 1995); in addition, many small flow voids in the basal ganglia and basal cistern corresponding to moyamoya vessels, infarction, gliosis, focal atrophy, and hemorrhage may be present. On MR angiography (MRA), occlusion of arteries and the formation of moyamoya arteries can be observed directly (Casselman et al. 1993; Houkin et al. 1994). However, in adults, it is difficult to differentiate between MMD and other diseases such as atherosclerotic stenotic disease by MRI and MRA alone. Advances in MRI have led to high anatomical and contrast resolution (Harada et al. 2001). In particular, 3-dimensional (3D) constructive interference in steady-state (CISS) MRI yields high-resolution images with good contrast between the cerebrospinal fluid and other structures (Casselman et al. 1993; Hirai et al. 2008; Yang et al. 2000). Although all cisternal structures such as arteries, veins, and nerves exhibit the same signal intensity on 3D-CISS images, they can be differentiated by following their anatomical course from the origin to the end (Yousry et al. 1999). Thus, more detailed studies using 3D-CISS images have been reported recently. Komiyama et al. report that 3D-CISS imaging can reveal moyamoya vessels in the basal cistern in over 90% of MMD patients. The purpose of this study was to clarify the characteristics of the ICA and middle cerebral artery (MCA) in MMD by using 3D-CISS and to analyze the pathological condition of these major vessels.
6. Materials and Methods

6-1 Patient Population

This study was approved by our institutional ethics review board. The study population consisted of 51 patients with MMD, 16 patients with atherosclerotic MCA stenosis and occlusion, and 70 control subjects. Between April 2008 and March 2011 they were diagnosed at the Department of Neurosurgery, Kumamoto University, Kumamoto, Japan. Their clinical data are summarized in Table 1. MMD was diagnosed by cerebral angiography studies according to the diagnostic criteria updated in 1997.2 The MMD patients consisted of 14 males and 37 females ranging in age from 10 to 73 years (mean 27.0 ± 16.7 years). Symptoms at MMD onset included ischemia (n = 46), hemorrhage (n = 2), headache, seizure (n = 1), and involuntary movements (n = 1). Sixteen patients with atherosclerosis (horizontal portion of the MCA [M1] stenosis, 10 cases; M1 occlusion, 6); the atherosclerotic group consisted of 11 men and 5 women ranging in age from 53 to 76 years (mean 57.9 ± 13.6 years). The MRI control group (n = 42) consisted of 24 men and 18 women ranging in age from 19 to 80 years (mean 54.0 ± 15.2 years); 33 had muscle contraction headache, and the other 9 had epilepsy without remarkable lesions on MR images. The digital subtraction angiography (DSA) control group (n = 28) consisted of 12 men and 16 women ranging in age from 20 to 75 years (mean 51.1 ± 13.2 years); 10 had posterior circulation unruptured small aneurysm, 8 had trigeminal neuralgia or facial spasm, 6 had epilepsy, and 4 had intracerebral cavernous angiomas.
Table 1

Summary of patients

<table>
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<tr>
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<th>Moyamoya group</th>
<th>Atherosclerosis group (M1 stenosis/occlusion)</th>
<th>MRI control group</th>
<th>DSA control group</th>
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<td>No. of patients</td>
<td>51</td>
<td>16</td>
<td>42</td>
<td>28</td>
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<td>Age (years ± SD)</td>
<td>27.0 ± 16.7</td>
<td>57.9 ± 13.6</td>
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<td>involuntary movement</td>
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*M* Values are mean ± SD.  DSA, digital subtraction angiography; M1, horizontal portion of the middle cerebral artery; MCA, middle cerebral artery
6-2 MRI Studies

All MRI scans were performed on a 3-T scanner (Magnetom Trio; Siemens, Erlangen, Germany) using 8-channel head coils. For imaging, we used 3-plane scout localizers, axial spin-echo T1-weighted (TR/TE/NEX, 450 ms/10 ms/1; matrix, 320 x 320), turbo spin-echo T2-weighted (TR/TE/NEX, 4060 ms/80 ms/1; turbo factor, 9; matrix, 512 x 512), and fast fluid-attenuated inversion recovery (FLAIR) (TR/TE/NEX, 9000 ms/120 ms/1; TI, 2500 ms; turbo factor, 15; matrix, 352 x 352), MRA and 3D-CISS sequences. Three-dimensional time-of-flight MRA was performed with the following parameters: TR/TE/NEX, 20 ms/3.5 ms/1; flip angle, 20°; section thickness, 0.5 mm; field-of-view (FOV), 200 mm; matrix, 512 x 208; and effective voxel size, 0.39 x 0.96 x 0.5 mm. Cephalad saturation pulses were applied to eliminate venous blood signals. Coronal imaging with a 3D-CISS sequence (TR/TE/NEX, 6.9 ms/3.4 ms/1; flip angle, 45°) was performed to evaluate the proximal portion of the intracranial arteries; the imaging parameters were matrix size, 512 x 512; FOV, 200 x 200 x 58 mm; and effective section thickness, 0.8 mm.

6-3 Outer and Inner Diameters of the Intracranial Arteries

All MMD and atherosclerosis patients underwent both MRI and DSA within 1 month. In our quantitative evaluation of the 3D-CISS images, two neuroradiologists (H.F. and T.H.) measured the outer diameters of the terminal portion of the ICA, the proximal portion of the M1, and the terminal portion of the basilar artery (BA) in the 3 study groups without knowledge of clinical information (Fig. 7). And we analyzed the ratios of outer diameters: ICA/BA and the M1/BA ratios. As the inner diameter of the vessels was not measured exactly on DSA films, we evaluated the inner diameter as the relative
value (%) compared to the ipsilateral IC-C5 portion diameter obtained from magnified DSA images on the anterior-posterior views (Fig. 7G and H). In addition, we analyzed the relationship between the outer diameters of the arteries on 3D-CISS and internal stenosis severity (% of IC-C5 portion) on DSA images by using scatter diagrams.

6-4 Statistical Analysis

All data are presented as the mean ± standard deviation (SD). All data were analyzed by Analysis of Variance (ANOVA). If significance was obtained, we used Scheffe’s criteria for multiple comparison. P < 0.05 was considered to be significant.
Fig. 7
A, B: Typical 3D-CISS MRI of a 58-year-old woman (control) diagnosed with tension-type headache. Coronal 3D-CISS MRI demonstrates no stenosis of the internal, middle cerebral, or basilar arteries. Arrows indicate the outer diameters of the terminal portion of the ICA (a), the proximal portion of the M1 (b), and the terminal portion of the BA (c) (the measuring points in this study).

C, D: A 47-year-old man with MMD who developed cerebral infarction and underwent left STA-MCA anastomosis. Coronal 3D-CISS MRI demonstrates narrowing of the outer diameters of the ICA (arrow) and MCA (double arrows). Lenticulostriate arteries are visualized relatively clearly (arrowheads). Outer diameter of the BA (D) is normal.

E: A 31-year-old woman with asymptomatic MMD. Coronal 3D-CISS MRI demonstrates narrowing of the outer diameters of the ICA (arrow) and MCA (double arrows) even in asymptomatic patient.

F: A 59-year-old man with atherosclerotic right M1 occlusion. Coronal 3D-CISS MRI demonstrates the outer diameter of the terminal portion of the ICA (arrow) and M1 (double arrows) are not narrow.

G, H: Right ICA DSA (anterior–posterior view) of the patients with epilepsy (G) and MMD (H). The luminal diameters of the IC-C5 portion (d and g); terminal portion of the ICA (e, h); and the proximal portion of the M1 were measured.
7. Results

7-1 Outer Diameters of the Cerebral Arteries

Table 2 shows the outer diameters of the vessels on 3D-CISS images in the 3 study groups. The mean outer diameters of the terminal portion of the ICA and the proximal portion of the M1 were significantly smaller in the MMD patients than those in the other 2 groups (P <0.01). There was no significant difference between the ICA and M1 with respect to side (data not shown). The outer diameter of the M1 in stenosis/occlusion did not differ significantly from that of the control. Furthermore, there was no statistically significant difference among the 3 groups with respect to the mean outer diameter of the BA. Next, we analyzed the ICA/BA and the M1/BA ratios (%); both ratios were significantly smaller in patients with MMD than in the control patients (P < 0.01), confirming that the outer diameters of both the ICA and M1 were significantly smaller in the MMD patients.

Table 2

Outer diameter on 3D-CISS imaging

<table>
<thead>
<tr>
<th></th>
<th>Moyamoya</th>
<th>Atheroscl.</th>
<th>Control</th>
<th>p value moyamoya vs. atheroscl.</th>
<th>p value moyamoya vs. control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 51)</td>
<td>(n = 16)</td>
<td>(n = 42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA (mm)</td>
<td>2.61 ± 0.46</td>
<td>4.32 ± 0.55</td>
<td>4.04 ± 0.50</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>M1 (mm)</td>
<td>1.92 ± 0.43</td>
<td>3.45 ± 0.56</td>
<td>3.34 ± 0.54</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BA (mm)</td>
<td>3.63 ± 0.61</td>
<td>3.81 ± 0.63</td>
<td>3.46 ± 0.48</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>ICA/BA ratio (%)</td>
<td>73.5 ± 15.3</td>
<td>114.2 ± 10.4</td>
<td>118.5 ± 19.2</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>M1/BA ratio (%)</td>
<td>53.7 ± 11.9</td>
<td>91.9 ± 16.1</td>
<td>98.0 ± 18.8</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Values are mean ± SD. 3D-CISS, three-dimensional constructive interference in steady state; atheroscl., atherosclerosis (middle cerebral artery stenosis/occlusion group); BA, basilar artery; ICA, internal carotid artery; M1, horizontal portion of the middle cerebral artery; NS, not significant. The numbers in () indicate the numbers of hemispheres.
7-2  Inner Diameters of the Cerebral Arteries

The DSA images of the 39 patients with MMD and 10 patients with M1 stenosis/occlusion were available for detailed evaluation. We excluded the MMD patients with cervical ICA occlusion or severe stenosis (>50% stenosis compared with the common carotid artery on DSA). Table 3 shows the inner diameter evaluation of the ICA and M1 (i.e., the percentage of the ipsilateral IC-C5 portion diameter) of the 3 groups. In patients with MMD, the inner diameters of the ICA and M1 were significantly smaller (P < 0.05) than those of the other 2 groups, except for the M1 diameter of the patients with MCA stenosis or occlusion.

Table 3
Angiographic evaluation of the inner diameter compared with the internal carotid artery C5 portion diameter on DSA

<table>
<thead>
<tr>
<th>Group</th>
<th>Side</th>
<th>% of IC-C5 diameter vs. moyamoya right side value</th>
<th>% of IC-C5 diameter vs. moyamoya right side value</th>
<th>p value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moyamoya</td>
<td>Rt.</td>
<td>41.6 ± 21.9</td>
<td>20.3 ± 17.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(n = 39)</td>
<td>Lt.</td>
<td>50.7 ± 20.3</td>
<td>19.1 ± 16.3</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Control</td>
<td>Rt.</td>
<td>82.6 ± 6.0</td>
<td>66.3 ± 5.9</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(n = 28)</td>
<td>Lt.</td>
<td>79.6 ± 6.6</td>
<td>64.0 ± 5.5</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Atheroscl.</td>
<td>Lesion</td>
<td>74.4 ± 8.3</td>
<td>26.7 ± 20.1</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>(n = 10)</td>
<td>Normal</td>
<td>70.8 ± 7.7</td>
<td>69.2 ± 4.3</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Values are mean ± SD (%). atheroscl., atherosclerosis (middle cerebral artery stenosis/occlusion group); DSA, digital subtraction angiography; ICA, internal carotid artery; M1, horizontal portion of the middle cerebral artery; NS, not significant.
7-3 Relationship between Outer and Inner Diameters

Using DSA image data, we analyzed the relationships between the outer and inner diameters of the vessels in the patients with MMD and M1 stenosis/occlusion by using scatter diagrams (Fig. 8). Interestingly, the outer diameters of the ICA and M1 were not related to the grade of inner diameter narrowing in MMD patients. Although all the inner diameters of the M1 in both groups were <60% of the IC-C5 portion, the M1 outer diameter of MMD patients was significantly smaller than that of the M1 stenosis/occlusion patients. According to these data, the borderline of the MCA outer diameter was 2.50 mm, which clearly distinguished MMD from atherosclerotic M1 stenosis/occlusion (MMD diagnostic sensitivity, 92.35%; 36 out of 39). Similarly, the borderline of the ICA outer diameter was 3.25 mm (sensitivity, 94.9%; 37 out of 39).
Fig. 8
Scatter diagram showing the correlation between the outer and inner diameters of the ICA(A) and M1(B) in the patients with MMD (n = 39) and M1 stenosis/occlusion (n = 10). The linear relationship and correlation coefficient ($R^2$) were analyzed in the patients with MMD. The dotted lines indicate the borderline of the ICA and MCA outer diameter, which clearly distinguished MMD from atherosclerotic M1 stenosis/occlusion.
8. Discussion

8-1 Outer-diameter narrowing of ICA and MCA in MMD

In this study, we demonstrated that in MMD patients, the outer diameters of the terminal portion of the ICA and the proximal portion of the M1 are significantly smaller than those of the normal control and atherosclerotic disease patients using coronal 3-D CISS MRI. We could evaluate the terminal portion of the ICA and the proximal portion of the M1 at the same time from coronal view. In contrast, the outer diameter of the M1 in patients with atherosclerosis was normal, while that of MMD patients became smaller, and this change was unrelated to the inner diameter narrowing stage.

As the mean age of the MMD patients was lower than those in the other 2 groups, we considered the possibility that 3D-CISS imaging detected smaller arteries in younger patients. In MMD, the occlusive lesion is always located in the anterior circulation; the posterior circulation is occasionally involved, while the vertebral artery and BA are rarely involved (Kinoshita et al. 1998; Li et al. 2009). The mean outer diameter of the BA in the MMD patient group was similar to those in the other older patient groups and the ICA/BA and the M1/BA ratios were lower than those in the other groups. Therefore, our findings suggest that the narrow outer diameters of the ICA and M1 are characteristic features of MMD. Based on intraoperative findings, Kuroda and Houkin also suggest that the ICA undergoes narrowing in MMD. Stenotic lesions of the extracranial ICA are seen in some cases with MMD, indicating that the narrowing of the outer diameters of the ICA and M1 may occur due to flow reduction (Yang et al. 1997; Yasaka et al. 2006). Thus, in this study, we excluded patients with cervical IC occlusion and severe stenosis and analyzed the relationship between the inner and outer diameter in each case.
8-2 Is arterial constrictive remodeling a major pathogenesis?

Scatter diagram analysis (Fig. 8) shows that the outer diameter of the M1 or ICA is obviously smaller in MMD patients than that in atherosclerosis patients. The pathogenesis of the arterial narrowing in atherosclerosis and MMD is fundamentally different. Intimal thickening, plaque development and resultant stenosis of the lumen are pathologic findings in patients with atherosclerosis (Glagov et al. 1987). On the other hand, the pathologic findings in the ICA and MCA of MMD patients indicate eccentric intimal fibrous thickening; such intimal lesions were often multilayered with newly formed elastic lamina between the layers (Fukui et al. 2000; Hosoda et al. 1997; Takekawa et al. 2004). The internal elastic lamina was markedly tortuous with duplication and a decreased number of smooth-muscle cells in the media (Fukui et al. 2000; Hosoda et al. 1997; Takekawa et al. 2004). These changes were observed around the terminal portion of the ICA and the proximal portions of the anterior cerebral artery and MCA but exhibited different patterns (Fukui et al. 1997; Hosoda et al. 1997; Ikeda et al. 1993; Takekawa et al. 2004). Interestingly, the narrowing of the outer diameter of ICA and MCA in MMD was unrelated to the progression of luminal stenosis and occlusion on DSA images (Fig. 8), indicating that the narrowing of the outer diameter in MMD patients exhibiting even mild stenosis on DSA. We hypothesize that the marked narrowing of the outer vascular diameter may precede internal vascular stenotic progression. How could the narrowing of the outer diameter in MMD be due to merely reflections of decreased flow? In studies of coronary arteries, two arterial remodeling modes were found: outward (positive) remodeling and constrictive (negative) remodeling. The outward remodeling results in the enlargement of vessel and is strongly associated with acute cardiac syndrome and plaque rupture, whereas
constrictive remodeling results in the constriction of vessel and is more common in patients with stable angina (Schoenhagen et al. 1993; Varnava et al. 2002). Li et al. found 2 cases showing constrictive (negative) remodeling of MCA, showing the similar MRI finding as our study, which were clearly different from typical atherosclerosis. Thus our findings may indicate that the constrictive remodeling is also present in intracranial arteries in MMD. We assume not only reflections of decreased flow but also constriction of the tortuous internal elastic lamina could be the narrowing of the outer diameter in MMD and may be an important phenomenon in MMD progression (Fig. 9). The pathologenesis of MMD is still unclear. Because it is difficult to obtain the specimen of intracranial arteries, we neurosurgeon could not compare the neuroradiological imaging with pathology, and the impossibility of performing a biopsy of the ICA or MCA in living patients prevents further study of its pathogenesis. Our study is the first to document a decrease in the outer diameters of the ICA and MCA in living MMD patients.

However, further research is necessary, and the development of imaging technology may assist in the study of this disease.
Fig. 9
The Schematic drawing of the progression patterns of arterial stenosis in moyamoya disease (MMD). The luminal diameter narrowing is mainly induced by constrictive change of affected artery
9. Conclusions

This is the first report indicate that decreases in the outer diameters of both the ICA and M1 occur with the decrease in inner diameter in MMD patients. Our findings suggest that the vascular constrictive changes of the affected arteries are important phenomenon in MMD progression. In addition, the detection of vessels exhibiting decreased outer diameters on 3D-CISS images may indicate a diagnosis of MMD.
10. References


Moyamoya disease at autopsy. *Virchows Arch A Pathol Anat Histol* 392:247-261


Takeuchi K, Shimizu K (1957) [Hypogenesis of bilateral internal carotid arteries]. No to Shinkei 9: 37-43


