Moyamoya Disease: A Review of Clinical Research

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About 5 decades have passed since the concept of moyamoya disease (MMD) was established in Japan. In that time, many clinical MMD studies have been performed from several different points of view, such as epidemiology, pathophysiology, surgical procedures, and prognosis. In addition, rapid developments in MMD genetic analysis have occurred. In light of all this activity, clinicians must continually update their knowledge of MMD in order to improve the prognosis of MMD patients. In this review article, we summarize the clinical MMD studies and introduce cutting-edge findings regarding MMD.

Key words: clinical research, moyamoya disease

In the 1960’s, Japanese neurosurgeons first described moyamoya disease (MMD), in the English literature, as a chronic occlusive cerebrovascular disorder characterized by bilateral stenosis of the supraclinoid portion of the internal carotid arteries with the formation of an abnormal vascular network at the base of the brain [1, 2]. The term “moyamoya” is derived from a Japanese expression for something hazy, like a puff of cigarette smoke drifting in the air (Fig. 1) [2]. Because the incidence of MMD is higher in East Asian than other populations [3], MMD research on pathophysiology and the development of surgical procedures have been conducted mainly in East Asian countries over the past 50 years. In this review article, we introduce cutting-edge findings pertaining to the diagnosis criteria, epidemiology, genetic factors, symptomatology, radiographic assessment, pathophysiology, treatment and prognosis of MMD.

Diagnostic Criteria

For a number of years, we used the criteria proposed by the Research Committee on Spontaneous Occlusion of the Circle of Willis in 1997 [4]. The criteria consisted of three principal factors as follows: (1) stenosis or occlusion at the terminal portion of the internal carotid artery (ICA) and/or at 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) lesion bilaterality [4]. The diagnostic criteria were modified in 2015, for the first time in about 20 years. The new diagnostic criteria followed the basic outlines of the criteria proposed in 1997, but with the key modification that the “bilaterality” was omitted. The newer criteria reflect the fact that it is necessary to perform cerebral angiography in patients with unilateral lesions or atherosclerotic lesions.

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Epidemiology

The prevalence of MMD has an ethnic bias with a high MMD incidence in countries in Eastern Asia, such as Japan and Korea [3]. In 2003, a nationwide survey in Japan estimated that the total number of patients treated was 7,700 and that the prevalence and annual rate of newly diagnosed cases were 6.03/100,000 and 0.54/100,000 population, respectively [5]. The sex ratio (female-to-male) was 1.8, and the peak of prevalence was in patients aged 10 to 14 years for females and in patients aged 20 to 24 years for males [5]. The prevalence of a family history of MMD was reported to be 12.1% [5]. In a total of 11,402 healthy subjects who underwent a brain check-up, the percentage of subjects with asymptomatic MMD was reported to be 0.07%, and its prevalence was estimated in the Japanese population as 50.7/100,000 people [6]. This prevalence is about 10 times as high as that reported in 2008 [5], which indicates that there are potentially many patients with MMD in Japan.

Genetic Factors

Mineharu et al. investigated 15 highly aggregated Japanese families (52 patients) to determine the inheritance pattern of familial MMD [7]. They reported that among a total of 135 offspring of affected people, 59 were patients with MMD or obligatory carriers and concluded that the mode of familial MMD inheritance was autosomal dominant with incomplete penetrance [7]. Genetic analysis of MMD has developed remarkably and rapidly in recent years [8]. Since the 1990s, several genome-wide linkage analyses have been performed, and the sole locus that has been confirmed is located at 17q25 [8]. Among the most important genetic discoveries is that ring finger protein 213 (RNF213), located in chromosome 17q25.3, is a susceptibility gene for MMD and the p.R4810K missense variant in the RNF213 increases its susceptibility to MMD in East Asian populations [9]. It has been reported that the homozygous c.14576G>A variant of RNF213 was correlated with some clinical manifestations of MMD, such as younger age at onset, severity of ischemia (cerebral infarction), and steno-occlusive change of the posterior cerebral artery (PCA) [10]. It is possible that bilateral progression may be associated with the number of risk alleles in RNF213 in unilateral MMD patients [11]. Vascular endothelial growth factor (VEGF) and kinase insert domain containing receptor (KDR; one of the VEGF receptors) polymorphism have also been reported to influence the age of onset and formation of synangiosis-induced collateral vessels after bypass surgery [12]. These data indicate that the clinical manifestation of MMD depends on genetic factors and suggest a new approach to MMD pathophysiology. In Caucasian
MMD patients, no association was found between MMD and the p.R4810K variant in RNF213 [13]. Some studies conducted in central Europe MMD patients have demonstrated significant associations with polymorphisms located in platelet-derived growth factor receptor beta and transforming growth factor beta 1 genes and with a polymorphism located in proline-serine-rich coiled-coil 1 [14, 15].

Symptomatology

There are 2 main types of symptoms: ischemia and hemorrhage. The distribution of these types differs between children and adults. Most children with MMD develop ischemic complications, such as transient ischemic attack and cerebral infarction, and approximately half of the adult patients have intracranial hemorrhage; the other half have ischemic complications [3]. In adult patients with MMD who are 40 years of age or older, the hemorrhagic type exceeds the ischemic type [16]. The most common symptom in ischemic MMD patients is motor disturbance, and that in hemorrhagic MMD patients is consciousness disturbance [16]. In MMD, symptoms in the same category—ischemic or hemorrhagic—usually recur, although it is rare for both types to occur in one patient. Hishikawa et al. revealed that 9% of MMD patients experienced a stroke type involving both ischemia and hemorrhage, and these 2 types of stroke showed both acute and chronic duration [17]. In this section, we introduce 2 symptoms, headache and involuntary movement, which are specific to MMD.

Headache. About 20% of MMD patients exhibited headaches as a symptom, including a disproportionately large group of pediatric and younger MMD patients. The headaches that accompany MMD are vascular in origin with migrainous features, which can cause impairment of daily life activities in MMD patients. A decrease in cerebral blood flow (CBF) or cerebrovascular reserve and spreading cortical depression have been reported as possible mechanisms of the headaches in MMD patients, and it has been demonstrated that revascularization can alleviate the headaches by improving perfusion pressure and cerebral circulation [18].

Involuntary movement. Various kinds of involuntary movement including chorea, choreo-athetosis, dyskinesia, dystonia, limb-shaking, and epilepsy-partialis continua, are seen in MMD patients [19], with the representative movement being chorea. Females are more frequently affected by chorea than males, and pregnancy has been reported to be a risk factor for involuntary movement associated with MMD [19]. Underlying mechanisms such as ischemia of the basal ganglia-thalamocortical circuits, increased sex hormones during pregnancy or due to the intake of oral contraceptive, and hyperthyroidism have been proposed [19]. Haloperidol is effective for controlling the choreic movements and revascularization surgery has been suggested to be beneficial because it normalizes the cerebral hypoperfusion [19].

Radiographic Assessment

Cerebral angiography. Cerebral angiography is the gold standard both for diagnosing MMD and assessing its progression. The most popular and traditional classification is Suzuki’s grading system [2]. According to Suzuki’s grading system, angiographic findings of MMD are classified into 6 categories (Table 1), and this classification is based on the temporal serial changes in the degree of development of

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tr>
<td>Stage 1</td>
<td>Narrowing of carotid fork</td>
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<tr>
<td>Stage 2</td>
<td>Initiation of the moyamoya and dilatation of intracranial main arteries</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Intensification of the moyamoya and defects of the ACA and MCA</td>
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<tr>
<td>Stage 4</td>
<td>Minimization of the moyamoya and defects of the PCA</td>
</tr>
<tr>
<td>Stage 5</td>
<td>Reduction of the moyamoya and development of ECA collaterals</td>
</tr>
<tr>
<td>Stage 6</td>
<td>Disappearance of the moyamoya and circulation only via ECA and VA</td>
</tr>
</tbody>
</table>

*Data are from Suzuki and Takaku [2].

ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; ECA, external carotid artery; VA, vertebral artery.
moyamoya vessels [20]. That is, Suzuki’s grading system could indicate the compensatory nature of MMD, where the external carotid artery (ECA) system complements the steno-occlusive change in the ICA system [21]. Mugikura et al. proposed a new grading system by modifying Suzuki’s grading system and reclassified the angiographic findings on the basis of the severity of steno-occlusive lesions in the proximal part of the ACA/MCA and the degree of antegrade opacification their branches (Table 2) [22]. This grading system is more useful for the precise staging of ICAs on a single angiography without the use of temporally serial angiographies as required by Suzuki’s grading system [20]. Both Suzuki’s grading system [2] and the system modified by Mugikura et al. [22] are classifications for anterior circulation (ICA, middle cerebral artery (MCA), and anterior cerebral artery (ACA)) involvement, and Mugikura et al. also reported a classification for posterior circulation (PCA) involvement [23].

Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA). Because of the rapidly growing prevalence and recent advancement of MRI in Japan, MMD can only be definitively diagnosed using MRA with the MRA-based diagnostic criteria. Houkin et al. established the MRA scores based on the severity of ICA, MCA, ACA, and PCA involvement and reported that they correlated well with Suzuki’s grading system [24]. Ryoo et al. demonstrated that 3-Tesla MRI wall imaging was useful in distinguishing MMD from atherosclerosis [25].

Positron emission tomography (PET) and single photon emission computed tomography (SPECT). PET and SPECT are necessary to assess hemodynamics in MMD patients. Some PET studies have reported that pediatric MMD patients have an increased regional oxygen extraction fraction (rOEF) relative to adult MMD patients [26] and the cerebral oxygen metabolism improves in pediatric and younger adult MMD patients without parenchymal lesions after bypass surgery [27]. In SPECT studies, it has been reported that MMD patients with low CBF at rest or with low vasodilatory capacity are prone to experience recurrent ischemic stroke [28] and basal/acetazolamide brain perfusion SPECT performed at 6 to 12 months after bypass surgery could predict further clinical outcomes of pediatric MMD patients [29].

Pathophysiology

MMD pathophysiology is closely related to both angioarchitecture and hemodynamics. Suzuki’s grading system represents the interaction between the ICA and ECA systems. Hishikawa et al. reported that steno-occlusive lesions in ICAs ipsilateral to PCAs with lesions are significantly advanced stages compared with lesions in ICAs ipsilateral to PCAs without lesions in MMD patients (Fig. 2) [20]. These data indicates that there is another important interaction in MMD between the anterior (ICA, MCA, and ACA) and posterior (PCA) circulation [23]. Miyamoto et al. first reported that there was a correlation between posterior circulation involvement (steno-occlusive lesions of PCA) and the severity of ischemia in MMD [30]. In addition, Yamada et al. demonstrated that the degree of steno-occlusive lesions of PCA significantly decreased regional CBF in the affected hemisphere, but Suzuki’s grades had no impact on regional CBF [31]. This may be explained mainly by a decrease in the leptomeningeal collaterals from the PCA to the anterior circulation [23]. The clinical significance of posterior circulation involvement in MMD is similar between pediatric and adult patients, with the only significant difference being that less advanced ICA lesions could complicate the posterior

<table>
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<th>ICA stage</th>
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<tr>
<td>I</td>
<td>Mild to moderate stenosis around ICA bifurcation with absent or slightly developed moyamoya</td>
</tr>
<tr>
<td>II</td>
<td>Severe stenosis around ICA bifurcation or occlusion of either ACA or MCA with developed moyamoya</td>
</tr>
<tr>
<td>III</td>
<td>Occlusion of both ACA and MCA with developed moyamoya</td>
</tr>
<tr>
<td>IV</td>
<td>Complete occlusion of both ACA and MCA with absence of or a small amount of moyamoya</td>
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</tbody>
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**Data are from Mugikura et al. [22].**

ICA, internal cerebral artery; ACA, anterior cerebral artery; MCA, middle cerebral artery.
circulation involvement in pediatric patients [20, 32, 33, 34]. There may be 2 patterns of interaction between the anterior and posterior circulation: an early and a delayed form of interaction. In patients with an early interaction, posterior circulation involvement complicates less advanced anterior circulation involvement and causes symptoms during childhood. In patients with a delayed interaction, posterior circulation involvement is correlated with advanced anterior circulation involvement and causes onset during adulthood. This hypothesis may explain the pathophysiology of the onset age biphasic pattern in MMD.

**Treatment**

*Evidence for MMD treatment.* Traditionally, surgical revascularization has been performed on ischemic MMD patients and its preventive effect on recurrent ischemic stroke has been demonstrated [35, 36]. According to the 2015 Japanese guidelines for the management of stroke, surgical revascularization is recommended for the ischemic type of MMD. The preventive effect of surgical revascularization on rebleeding in hemorrhagic MMD patients has been debated for many years [37, 38]. The Japan Adult Moyamoya trial (JAM trial), a multicenter randomized controlled trial, reported in 2014, provided information on the therapeutic strategy for hemorrhagic type MMD [39]. There was a significant difference between the surgical and nonsurgical groups, suggesting that direct bypass had a preventive effect against rebleeding based on a Kaplan-Meier analysis [39]. Takahashi et al. also showed that the MMD patients with posterior hemorrhage were at higher risk of rebleeding and accrued greater benefit from bypass surgery in a subgroup analysis of the JAM trial [40]. The JAM trial results suggested that surgical revascularization should be considered for hemorrhagic MMD patients in the 2015 Japanese guidelines for the management of stroke.

*Surgical procedures.* The surgical procedures for MMD include direct bypass, indirect bypass and combined bypass. The most popular procedure, direct bypass, involves superficial temporal artery to MCA (STA-MCA) anastomosis [41]. STA-ACA and occipital artery (OA)-PCA bypass procedures have been reported for the ACA and PCA territory [42, 43]. Many indirect bypass procedures using various kinds of tissues as blood supply sources have been reported, including encephalo-duro-arterio-synangiosis (EMS) [44], encephalo-duro-arterio-synangiosis (EDAS) [45], the multiple burr hole surgery technique [46], ribbon encephalo-duro-arterio-myo-synangiosis (EDAMS) [47], encephalo-duro-myo-arterio-pericranio-synangiosis (EDMAPS) [48], and omentum transplantation [49]. Mizoi et al. showed that a patient’s age appears to affect the development of collateral formation from indirect bypass and that the direct bypass procedure should be the first-line surgical treatment option for
adult MMD patients [50].

Perioperative management. There are some issues particular to perioperative management of MMD and overcoming these issues leads to good surgical outcomes. Carbon dioxide is an important chemical mediator of cerebral vessels. Both hypercapnia and hypocapnia can induce a reduction of regional CBF through the mechanism of vasoconstriction and steal phenomenon via vasodilation, respectively. Maintaining normocapnia is highly desirable for MMD perioperative management in order to prevent ischemic complications, especially in children [51]. A relatively high percentage of MMD patients experience transient neurological deficits in response to various hemodynamic changes in the postoperative course of direct bypass surgery during the acute phase. Hypoperfusion is related to competing blood flows from the collateral circulation, new blood flow from the STA, and impaired cerebral autoregulation [52]. Fujimura et al. reported that about one-fourth of MMD patients who underwent direct bypass surgery experienced symptomatic hyperperfusion and that adult-onset and hemorrhage-onset patients had a higher risk of symptomatic hyperperfusion [53]. A PET study revealed increases in the CBF and cerebral blood volume (CBV) and a decrease in OEF during hyperperfusion [54]. A preoperative increase in OEF [54] or CBV [55] has been reported to be a risk factor of hyperperfusion from the hemodynamic point of view. A de novo ivy sign, which refers to a linear high-signal intensity along the cortical sulci or brain surface on a fluid-attenuated inversion recovery image, could be useful in detecting postoperative hyperperfusion [56]. Minocycline hydrochloride, known as an inhibitor of matrix metalloprotease 9, may, with strict blood pressure control, prevent symptomatic hyperperfusion [57].

Surgical outcome. A review that included data from 1,448 surgically-treated pediatric MMD patients showed that the rates of perioperative stroke and reversible ischemic events were 4.4% and 6.1%, respectively, and 87% of the patients experienced complete disappearance of or reduction in symptomatic cerebral ischemia [35]. Kazumata et al. reported that the prevalence of postoperative stroke related to direct/combined revascularization in adult MMD patients was significantly higher than that in pediatric MMD patients [58]. Moreover, they showed that in pediatric MMD patients, perioperative stroke was significantly more frequent in indirect bypass compared with direct/combined bypass and that in adult MMD patients, there were no significant differences in postoperative stroke between direct/combined bypass and indirect bypass [58]. These data mean that the surgical procedures and the patient’s age may have an influence on perioperative stroke.

Prognosis

The prognosis of young pediatric MMD patients, especially those younger than 4 years of age, is poor because of the high prevalence of cerebral infarction [59]. Possible mechanisms underlying cerebral infarction in patients diagnosed before four years of age are the high frequency of steno-occlusive lesions of the PCA, poor development of transdural collaterals, and a relatively insufficient blood supply to the developing brain [59]. In a long-term follow-up study, pediatric patients with MMD showed a comparable rate of good social adaptation in adulthood [60], but Funaki et al. demonstrated that PCA involvement could be an underlying risk factor for unfavorable social outcome [61]. In adult MMD patients with ischemic symptoms, PCA involvement at the initial onset was significantly correlated with poor outcome, and revascularization of the MCA territory in patients with PCA involvement was effective at preventing recurrent ischemic stroke [62]. The prognosis of hemorrhagic MMD patients who undergo conservative treatment is unsatisfactory and the most important factor related to the poor prognosis is rebleeding. Kobayashi et al. demonstrated that the annual rebleeding rate was 7.09%/person/year and after rebleeding the mortality rate rose 6.8% to 28.6% [63]. The JAM trial showed the preventive effect of direct bypass surgery against rebleeding in hemorrhagic MMD patients, but its mean follow-up period was only 4.32 years [39]. Whether the preventive effect of direct bypass surgery against rebleeding will continue for a longer period needs to be investigated.

Conclusions

We reviewed cutting-edge findings on the diagnosis, epidemiology, genetic factors, pathophysiology, treatment, and prognosis of MMD. This article is
intended to be useful to all neurosurgeons, neuroradiologists, pediatricians, anesthesiologists and neuroradiologists who participate in the management of patients with MMD.

References