Epidemiology, diagnosis and treatment of moyamoya disease (Review)

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Abstract. Moyamoya disease (MMD) is a type of chronic cerebrovascular occlusion disease, which frequently occurs in East Asian populations, including pediatric and adult patients, and may lead to ischemic or hemorrhagic stroke, headache, epilepsy or transient ischemic attack. To date, the underlying mechanisms of MMD have remained to be fully elucidated, but certain studies have indicated that genetic factors may be an important component of its development. Cerebral angiography is the best approach for diagnosing MMD. However, with technological advances, non-invasive techniques are increasingly used to accurately evaluate MMD. MMD is commonly treated via surgery, and an increasing number of patients are benefitting from the intra- and extra-cranial revascularization. The present article provides a comprehensive review of MMD on the basis of previous research.

Contents

1. Introduction

Moyamoya disease (MMD) is a type of chronic occlusive cerebrovascular disease. The pathogenetic mechanisms remain to be fully elucidated. Its major characteristic is a steno-occlusive change at the end of the internal carotid artery (ICA), middle cerebral artery (MCA) and/or proximal anterior cerebral artery (ACA), which is accompanied by the formation of smoke-like abnormal blood vessels in the base of the skull in digital subtraction angiography (DSA). In 1957, Takeuchi and Shimizu described the pathological manifestation of MMD for the first time for bilateral hypoplasia of the ICA (1). Cerebral angiography in such patients reveals smog-like blood vessels in the skull base, which was officially named MMD by Suzuki and Takaku (2) in 1969. The incidence of MMD is high in East Asian populations but low in European and North American populations (3). The clinical signs of MMD mainly include two types: Cerebral ischemia and cerebral hemorrhage. These two types of symptom differ in their distribution between pediatric and adult patients. Most of the pediatric patients present with progressive cerebral ischemia, including transient cerebral ischemic attacks and cerebral infarctions. Mental decline or seizures may be the first symptom in children. In half of the cases in adults, intracranial hemorrhage is the first symptom, while ischemic symptoms first occur in the other half (3). In recent years, large amounts of research on the diagnosis and treatment of MMD have been performed in China, Japan and South Korea. The present article provides a review of the relevant domestic and international literature for the following aspects of MMD: Diagnosis, clinical symptoms, epidemiology, genetics, radiographic evaluation, pathology and treatment methods.

2. Diagnostic criteria and clinical symptoms of MMD

In 1996, Japan issued a guide for the diagnosis and treatment of the spontaneous occlusion of the circle of Willis ('Moyamoya' disease, MMD) (4), which suggests the following manifestations on cerebral angiography i) Stenosis or occlusion at the end of the carotid artery, the proximal ACA and/or MCA; ii) an abnormal vascular network in the vicinity of stenotic occlusion lesions in the arterial phase; and iii) the above manifestations are bilateral (Fig. 1). In 2012, the latest guidelines for the pathology and treatment of MMD on the basis of the 1997 guidelines were published in Japan; the 1997 diagnostic criteria were revised in these novel guidelines (5). In the 2012 guidelines, cerebral angiography remains the gold standard for the diagnosis of MMD with the staging performed according to angiographic findings (Table I). The novel guidelines added a staging based on scores of magnetic

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resonance (MR) angiography (MRA) and the diagnostic criteria are as follows: i) Stenosis or occlusion at the end of ICA and/or the initial segment of the ACA and/or MCA. ii) At least two obvious shadows of the blood flow are displayed on the same scan level at the basal ganglia region, suggesting the existence of an abnormal vascular network. iii) The above manifestations are bilateral, but bilateral lesions may be staged differently (Table II). In the evaluation system, the MRA results are simply scored and totaled. A total score of 0-1 represents stage 1, which indicates DSA I and II; a score of 2-4 represents stage 2, which indicates DSA III; a score of 5-7 represents stage 3, which indicates DSA IV; and a score of 8-10 represents stage 4, which indicates DSA V and VI.

According to the new guidelines, differential diagnoses of MMD, which should be excluded, are the following underlying cerebrovascular diseases: Atherosclerosis, autoimmune diseases, meningitis, brain tumors, Down syndrome, Recklinghausen's disease, head injury and cerebrovascular damage after head irradiation. Recently, a Chinese experts' consensus on the diagnosis and treatment of MMD and MM syndrome (MMS) was published (6), which argues that the identification of MMD and MMS lacks molecular markers or other characteristic objective indicators. Instead, the identification of MMS and MMD diagnoses mainly depends on morphological characteristics and the exclusion of other diseases in which one of the main symptoms is the presents of smoke-like abnormal blood vessels, which is not feasible to perform in the clinic. In most cases, there is no significant difference in principles of treatment between MMD and MMS. For the diagnosis and treatment options for patients with suspected MMS, it is possible to refer to the guidelines for MMD.

The clinical symptoms of MMD include transient ischemic attacks, ischemic stroke, hemorrhagic stroke, epilepsy, headache and cognitive dysfunction, with the incidence of each symptom varying depending on the age of the patient (5). MMD has two major symptoms: Cerebral ischemia and cerebral hemorrhage. Most pediatric patients with MMD are characterized by progressive cerebral ischemic symptoms, including transient ischemic attack and cerebral infarction, mental decline, seizures and involuntary movements. About half of all adult patients present with intracranial hemorrhage, and the other half with ischemic symptoms (3). In adult patients aged >40 years, the hemorrhagic type is more common than the ischemic type. The most common symptom for patients with ischemic MMD is dyskinesia, and an impaired consciousness is the most common symptom for those with hemorrhagic MMD (7). For each of the two types of MMD, cerebral ischemia or cerebral hemorrhage is often recurrent, but these two signs rarely occur in the same type of patient with MMD. Cerebral ischemia and transient ischemic attack are common in North American and European patients, while Asian patients often suffer from intracranial hemorrhage as the first symptom (5,8-11). However, according to certain experts, MMD is mainly ischemic in China (12).

Among pediatric patients (under 14 years old) with MMD, ~20% suffer from headache. Seol *et al* (13) reported that 44 of 204 (21.6%) pediatric patients with MMD complained of headaches. At present, it is thought that headache may occur due to the reduction of cerebral blood flow or cerebral blood flow reserve and diffusive cortical inhibition. Headache symptoms may be relieved by improving cerebral vascular perfusion (14).

3. Epidemiology of MMD

The incidence of MMD exhibits significant regional differences, with a high incidence in East Asia and a low incidence in other regions. According to previous studies, the prevalence of MMD is 10.5/100,000 individuals and the incidence rate is 0.94/100,000 individuals in Japan (15); in South Korea, the prevalence rate is 16.1/100,000 and the incidence rate is 2.3/100,000 individuals (16). The incidence of MMD was as low as 0.09/100,000 individuals in other regions, including North America, but it has exhibited an upward trend in the US (17). In Nanjing (China), the prevalence of MMD in the time frame of 2000-2007 was 3.92/100,000 (18). According to the most recent study, 2,430 cases of MMD have been reported in China since 1976 (12).

Worldwide, the age of onset of MMD is significantly bimodal in distribution, with a bimodal peak consisting of a major peak in the first decade of life and a moderate peak in the late 20 to 30s (4-6,12,15-19). Of note, geographic differences in sex distribution have been observed. In foreign populations, the incidence of MMD in females was reported to be higher than that in males with the male-to-female ratio ranging from 1:1.8 to 1:2.2 (5,15-17); however, the sex ratio is 1:1 in China (12,18,19).

4. Genetic factors associated with MMD

MMD has been reported to have an increased prevalence in certain ethnicities and pedigrees (20), suggesting that genetic factors may be involved. Numerous studies have indicated that genetic factors have an important role in the pathogenesis of MMD (21-23). In 2011, a whole genome-wide association study (GWAS) on 72 patients with MMD by Kamada *et al* (24) identified a novel susceptibility gene, Ringin Protein 213 (RNF213), and indicated that this gene is highly associated with familial MMD. In the same year, Liu *et al* (25) also demonstrated the genetic susceptibility of RNF213 in patients with MMD in a GWAS on 8 MMD families. Subsequent studies have indicated that the presence of a low-frequency variation of RNF213 (c.14576G>A, p.R4810K) significantly increases the risk of MMD in Asian populations (26-28). RND213 p.R4810K mutations are divided into homozygous and heterozygous mutations; MMD patients with a homozygous mutation are characterized by an earlier onset, more severe symptoms and a worse prognosis. A study by Kim *et al* (29) on a Korean population revealed that in MMD patients with a RNF213 p.R4810K homozygous mutation, the age was <5 years, the disease mainly manifested as cerebral infarction and patients exhibited cognitive dysfunction. To date, RNF213 p.R4810K mutations have not been detected in European patients with MMD, but certain rare variants of RNF213 have been identified (28,30,31). According to the most recent study, RNF213 mutations other than p.R4810K have an important role in Caucasians with MMD (32).

Domestic genetic studies on MMD have been performed in succession. In a study by Li *et al* (33) from 2010, 208 cases of Han Chinese subjects with MMD and 224 control subjects

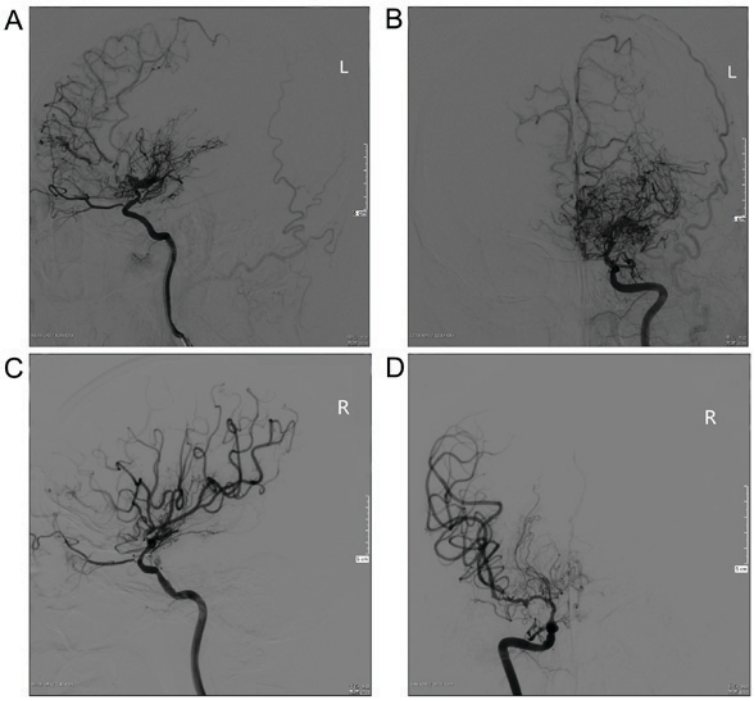

Figure 1. Representative cerebral angiography image of one patient with moyamoya disease. Internal carotid artery angiography: (A) Left lateral, (B) left Towne's position, (C) right lateral and (D) right Towne's position. The occlusion of the internal carotid artery was visible, and there a large number of 'smoke-like' vessels were present in the skull base. L, left; R, right; AO, anterior oblique views; CRA, cranial; CAU, caudal.

were assessed, revealing that a polymorphism of the 1,171 locus of the matrix metalloproteinase-3 gene was closely associated with MMD. In 2012, Wu *et al* (26) reported that in a population of 170 Han Chinese patients with MMD and 507 control subjects, a single-nucleotide polymorphism of the R4810K locus of the RNF213 gene was associated with a significantly increased risk of MMD, while that in another locus, A4399T, may be associated with hemorrhagic MMD.

5. Imaging assessment of MMD

Cerebral angiography is the gold standard for diagnosing MMD and assessing its progression. The system most widely used for its evaluation is the Suzuki staging system (2), in which the cerebral angiographic findings of MMD patients are divided into 6 stages (Table I). This staging system is based on the progression degree of smog-like blood vessels (34), and suggests that, in cases of stenotic-occlusive changes in the carotid artery system of MMD patients, a compensation of the intra-cranial cycle exists in the extracranial arterial system (35). In 2002, Mugikura *et al* (36) proposed a new staging system, which is a revised version of the Suzuki staging system, where re-staging is performed according to the severity of stenosis or occlusion in the MCA and the proximal ACA on cerebral angiography and the angiographic extent of their branches (Table III). The Suzuki staging system and the improved version by Mugikura *et al* (36) are used for staging of MMD according to the performance of the internal carotid artery. The same group has also proposed a classification involving the vertebral basilar artery in childhood MMD (37).

Brain MR imaging (MRI) is able to display the brain parenchymal lesions associated with MMD, and MRA is able to reveal abnormalities consistent with cerebral angiography. In 2005, Houkin *et al* (38) established a scoring system based on the degree of lesions of the ICA, ACA, MCA and posterior cerebral artery on MRA and claimed that this system was as suitable as the Suzuki staging system. This MRA scoring system was added to the 2012 Guidelines for the Diagnosis and Treatment of MMD in Japan (5). Ryoo *et al* (39) reported that high-resolution nuclear MRI is able to effectively distinguish between MMD and atherosclerosis based on differences in cerebral blood vessels.

Assessment of cerebral hemodynamics and the brain metabolism level is also an important part of the imaging assessment of patients with MMD. This assessment provides a more objective and realistic indicator for the selection and efficacy assessment of surgery regimens for MMD. In the current assessment of brain metabolism, positron emission tomography (PET) and single-photon emission computed tomography may be employed for detection. For the assessment of cerebral hemodynamics, computed tomography perfusion imaging and MR perfusion-weighted imaging may be applied (40-45).

6. Pathology of MMD

The basic pathology of MMD mainly includes intimal fibrous hyperplasia of the intracranial arterial stenosis, irregular proliferation of the inner elastic layer, thinning of the middle layer of the vessel wall and reduction of the outer diameter of the blood vessel (3,46). A high-resolution MRI cohort study indicated that most patients with MMD had a contractile remodeling at the distal end of the ICA and a long concentric enhancement (39). This result is consistent with the thickening of the arterial intima and the thinning of the tunica media detected by vascular pathology (47).

Table I. Stages and cerebral angiographic findings (5).

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

Table II. Classification and scoring based on the MRA findings (5).

A, Scoring for each artery

Score	MRA findings
Internal carotid artery	
0	Normal
1	Stenosis of C1
2	Discontinuity of the C1 signal
3	Invisible
Middle cerebral artery	
0	Normal
1	Stenosis of M1
2	Discontinuity of the M1 signal
3	Invisible
Anterior cerebral artery	
0	Normal A2 and blood vessels distal to A2
1	Signal decrease A2 and its distal blood vessels
2	Invisible
Posterior cerebral artery	
0	Normal P2 and blood vessels distal to P2
1	Signal decrease P2 and its distal blood vessels
2	Invisible

B, Total score calculated individually for the right and left side

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

MRA, magnetic resonance angiography.

Growing evidence supports the notion that MMD is essentially a vascular intimal hyperplastic disease. Histopathological analysis of the distal carotid artery indicated that the hyperplasia occurs in arterial wall smooth muscle cells and

Table III. Angiographic ICA staging system modified by Mugikura *et al* (36).

ICA stage	Angiographic findings
I	Mild to moderate stenosis around carotid bifurcation with absent or slightly developed ICA moyamoya: Almost the entire ACA and MCA branches are opacified in antegrade fashion
II	Severe stenosis around carotid bifurcation or occlusion of either of proximal ACA or MCA with well-developed ICA moyamoya: The ACA and/or MCA branches are clearly defective, but at least several of the ACA or MCA branches remain opacified in antegrade fashion
III	Occlusion of the proximal ACA and/or MCA with well-developed ICA moyamoya: Only a few of the ACA and/or MCA branches are faintly opacified in antegrade fashion through the meshwork of ICA moyamoya
IV	Complete occlusion of the proximal ACA and MCA with absent or small amount of ICA moyamoya: No opacification of either ACA or MCA branches in antegrade fashion

ACA, anterior cerebral artery; MCA, middle cerebral artery; ICA, internal carotid artery.

endothelial cells (48), and that the endometrial thickening caused by fibrous cell hyperplasia of the arterial intima is the cause of arterial stenosis and occlusion (3). Guo *et al* (49) reported that arterial stenosis and occlusion of familial MMD may be due to smooth muscle tissue hyperplasia associated with a mutation in the actin, α2, smooth muscle, aorta gene. Endothelial progenitor cells (EPCs) have an important role in maintaining blood flow in the infarct region of patients with ischemic stroke (50). Kim *et al* (51) reported that the angiogenic function of EPCs in patients with MMD is defective, which may be the cause of abnormal angiogenesis in patients with MMD. Lee *et al* (52) indicated that the expression of retinaldehyde dehydrogenase 2 was epigenetically inhibited in endothelial colony-forming cells (ECFCs) from patients with MMD, which may have a key role in the functional impairment of ECFCs.

Increased levels of multiple autoimmune antibodies in patients with MMD suggest that the immune response may be involved in the pathogenesis of MMD. Kim *et al* (53) identified that the levels of thyroid auto-antibodies were elevated in numerous patients with MMD. Sigdel *et al* (54) used protein chip technology to assess patients with MMD and identified a variety of auto-antibodies associated with MMD. In addition, numerous studies have indicated that multiple cytokines, including vascular endothelial growth factor, basic fibroblast growth factor, hepatocyte growth factor, cellular retinoic acid binding protein 1 and granulocyte-colony-stimulating factor, were present in the plasma, cerebrospinal fluid, dura mater, as well as arachnoid and superficial temporal artery of patients with MMD (46,55-58). Furthermore, chronic arterial inflammation caused by immune responses has been recognized as an important driver of the progression of MMD (54). However, the molecular mechanisms underlying the involvement of the immune response in MMD have remained to be fully elucidated.

7. Treatment of MMD

At present, no evidence suggesting that drug treatment is able to delay or even reverse the progression of MMD is available. The current drug treatment for in MMD only targets its clinical symptoms, including ischemia and hemorrhage, by exerting anti-coagulant or hemostatic effects. The Japanese guidelines from 2012 recommend the use of anti-platelet aggregation drugs for the treatment of ischemic MMD (5), but the risk of bleeding remains.

Regarding the occurrence of ischemic stroke in patients with ischemic MMD, the preventive effect of surgical revascularization treatment has been clinically demonstrated (35,59-62). However, intra- and extra-cranial revascularization for the prevention of recurrence of bleeding in patients with hemorrhagic MMD is controversial. Duan *et al* (19) performed a review of patients with MMD and noted that the probability of recurrence of cerebral ischemia or cerebral hemorrhage in patients subjected to surgical re-vascularization was significantly lower than that in patients who received conservative treatment. A study on Japanese adults with MMD from 2010 defined the primary and secondary end points as all adverse events and rebleeding attacks, respectively. It was reported that for patients with hemorrhagic MMD, the difference between the surgical and non-surgical group was statistically significant, and a Kaplan-Meier analysis suggested that the collateral circulation provided by the surgery was able to prevent recurrent bleeding (63). Further studies have provided similar results (64,65). Therefore, the prevailing opinion is that patients with ischemic or hemorrhagic MMD should receive surgical treatment (66).

Surgical revascularization of MMD includes 3 types: Direct revascularization, indirect revascularization and combined revascularization. In the direct revascularization surgery, the most common method is superficial temporal artery-MCA anastomosis. When ischemic hypoperfusion occurs in the blood supply area of the ACA or posterior cerebral artery, the superficial temporal artery-ACA or occipital artery-posterior cerebral artery anastomosis may be adopted (67,68). Indirect revascularization is a surgery based on a variety of tissues used as a source of blood supply, mainly including encephalomyosynangiosis, encephaloduroarteriosynangiosis, multiple burr hole surgery, encephaloduromyoarteriosynangiosis, encephaloduromyoarteriopericranial synangiosis and omental transplantation (69-74). Combined revascularization refers to the combined use of the former two revascularization techniques. A recent meta-analysis revealed that direct

or combined revascularization surgery is better for unstable adult patients with MMD characterized by symptomatic or hemodynamic instability (75).

During the peri-operative period, it is necessary to actively prevent the occurrence of ischemic complications, particularly in pediatric patients with MMD (76). Most patients undergoing direct vascular bypass surgery in the acute phase may suffer from transient neurological dysfunction due to changes in hemodynamics. The brain tissue hypoperfusion caused by changes in hemodynamics is mainly caused by the competition between the blood flow from the superficial temporal artery bridge blood vessels and the blood flow from the existing collateral circulation, due to damage to the cerebrovascular auto-regulation function (77). Studies have indicated that ~1/4 of patients with direct bypass may suffer from high perfusion symptoms, and there was a high risk of high perfusion in adult patients with MMD and patients with hemorrhagic MMD (78). A PET study indicated that cerebral blood flow and cerebral blood volume (CBV) increased, while the oxygen extraction fraction (OEF) decreased under high perfusion (71). In terms of hemodynamics, the increase in pre-operative CBV or OEF is a risk factor for post-operative high perfusion (79,80). It is necessary to closely monitor the blood pressure fluctuations in patients during the peri-operative period, in order to prevent the occurrence of low or excessive perfusion.

8. Summary

The pathogenesis of MMD still remains to be fully elucidated. The worldwide incidence of MMD is low, but it has a higher incidence in Asian countries. MMD is an important cause of cerebral stroke in pediatric and adult patients. In order to avoid the occurrence of severe neurological symptoms, a definitive diagnosis of MMD must be made as soon as possible, so that treatment may be rapidly performed and a relatively good mid- and long-term prognosis may be achieved. Surgery remains an important treatment for MMD, but an individualized clinical treatment strategy should be selected according to the condition of each patient. With the increasing number of genetic studies, novel treatment approaches for MMD at the genetic level may be developed in the future.

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Authors' contributions

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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