Progression in Moyamoya Disease: Clinical Features, Neuroimaging Evaluation, and Treatment

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Abstract: Moyamoya disease (MMD) is a chronic cerebrovascular disease characterized by progressive stenosis of the arteries of the circle of Willis, with the formation of collateral vascular network at the base of the brain. Its clinical manifestations are complicated. Numerous studies have attempted to clarify the clinical features of MMD, including its epidemiology, genetic characteristics, and pathophysiology. With the development of neuroimaging techniques, various neuroimaging modalities with different advantages have deepened the understanding of MMD in terms of structural, functional, spatial, and temporal dimensions. At present, the main treatment for MMD focuses on neurological protection, cerebral blood flow reconstruction, and neurological rehabilitation, such as pharmacological treatment, surgical revascularization, and cognitive rehabilitation. In this review, we discuss recent progress in understanding the clinical features, in the neuroimaging evaluation and treatment of MMD.

Keywords: Epidemiology, genetic characteristics, Moyamoya disease, neuroimaging, pathogenesis, progression, treatment.

1. INTRODUCTION

Moyamoya disease (MMD) is a chronic cerebrovascular disease characterized by progressive stenosis of the terminal segment of the internal carotid artery and the circle of Willis, resulting in the formation of a collateral vascular network at the base of the brain [1]. The clinical manifestations of this disease are complicated. Since it was first reported in the 1950s, numerous studies [2-5] from different parts of the world have attempted to clarify its epidemiological characteristics in different regions. Furthermore, studies of its genomics and pathophysiology have also promoted understanding of the unclear etiology of this disease [6, 7]. With the development and application of radiological techniques, various neuroimaging methods with different advantages have furthered the understanding of MMD in terms of its structural, functional, spatial, and temporal aspects [8, 9].

At present, the main treatment for MMD focuses on neurological protection, cerebral blood flow reconstruction, and neurological rehabilitation, including pharmacological treatment, surgical revascularization, and cognitive rehabilitation [10-12]. In this review, we discuss recent advances in the understanding of its clinical features, its neuroimaging evaluation, and its treatment, to highlight prospective future directions in these fields.

2. EPIDEMIOLOGY

2.1. Incidence and Prevalence

MMD apparently has regional and ethnic characteristics. The incidence of MMD is higher in Asia than in Europe, America, Africa, and Latin America. Japan has a robust case-information registration mechanism and also has the highest incidence of MMD. According to 2 Japanese nationwide epidemiological surveys, the total number of patients diagnosed with MMD nearly doubled from 3,900 (95% confidence Interval [CI] 3,500-4,400) in 1994, to 7700 (95% confidence interval, 6,300-9,300) in 2003. During this time period, the prevalence and incidence rates increased from 3.16 and 0.35 per 100,000 population to 6.03 and 0.54 per 100,000 population, respectively, partly due to the development of neuroimaging techniques and improvement of the diagnostic criteria [13, 14]. Another epidemiology survey of unilateral MMD (typical angiographic evidence of MMD unilaterally, with equivocal contralateral findings) and quasi-MMD (MMD present with inherited or acquired disorders) conducted in 2013 estimated that there were about 6671
MMD patients, 841 unilateral MMD patients, and 430 quasi-MMD patients in Japan. The annual incidence rates of MMD, unilateral MMD, and quasi-MMD were estimated as 1.13, 0.23, and 0.11/100,000, and the prevalence rates as 5.22, 0.66, and 0.34/100,000, respectively [15].

Other southeast Asian regions, like China and South Korea, have also reported high incidences of MMD. A South Korean nationwide and population-based study estimated the number of patients with MMD to be 8,154 in 2011 and the incidence increased from 1.7 to 2.3 per 100,000 population from 2007 to 2011 [16]. A regional multi-center epidemiological survey by 15 hospitals in Nanjing, China, suggested that prevalence and incidence rates of MMD were 3.92 and 0.43/100,000 during a 12-year period [17]. In Taiwan, China, an investigation by 7 hospitals revealed that the average incidence rate was 0.48/100,000 during a 12-year period [18]. In addition, a recent epidemiological single-center study in China identified 4,128 patients with MMD, with the highest prevalence observed in the Central Plains and surrounding regions, such as Henan province (0.88/100,000), Hebei province (0.818/100,000), Beijing (0.765/100,000), and Shandong province (0.660/100,000) [19].

Relatively lower incidence and prevalence rates of MMD were reported in Europe. For example, a Danish population-based study indicated an incidence rate of 0.07 per 100,000 person-years from 2008 onwards [2]. The prevalence of MMD among Irish Caucasians was calculated as 0.33/100,000, with a mean annual incidence of 0.04/100,000 [20]. America presented varying incidence rates of MMD in its different regions. Incidences in the USA ranged from 0.05/100,000 in Iowa, and 0.086/100,000 in Washington State and California, to 0.17/100,000 in Hawaii, per 100,000 patient-years [21-24]. Approximately 7,473 patients had been diagnosed with MMD in the USA from 2005 to 2008 [25]. Literature from different regions all over the world is compared in Fig. (1).

2.2. Age Distribution

Relative studies have suggested that the youngest patient diagnosed with MMD could be less than 4 years old [14, 16]. In Japan, previous studies have suggested that there are 2 peaks of MMD in terms of age distribution: approximately 10-19 years and 40-49 years [13]. However, these values were modified in the 2003 nationwide epidemiological survey, which revealed 3 peaks in men: 10-14 years, 35-39 years, and 55-59 years, and 2 peaks in women: 20-24 years and 50-54 years [14]. While in Korea, the first peak occurred at age 15-19 years and the second peak occurred at age 50-59 years [16]. Three epidemiological studies conducted in China revealed the same age distribution peaks in pediatric patients, i.e., 5-9 years, but differed in the peak for adult patients, i.e., 40-44 years in both sexes, in Taiwan, China, and 35-39 years, in Nanjing province and the Central Plains and surrounding regions [17-19].

MMD patients of European Caucasian ethnic background demonstrated a tendency to present at a younger age: 35.8 ± 14.8 (range 1.6-72 years) [26]. Among patients enrolled in a German retrospective study, the youngest patient was reported to be 1 year old, while the median age of onset was 32.9 years (median 32 years, range 1-74 years, standard deviation 14.04 years) [27]. A long-term follow-up study in a Finnish population revealed that the mean age at the start of the follow-up ranged from 3 to 77 years (with a median age of 35 years) [28].

In the USA, there was a single age peak, at 1-10 years, in Iowa, while there was another peak, at 55-59 years, in California and Washington [23]. The age of onset also differed by ethnicity, as African Americans demonstrated an earlier onset, with a median age of onset of 18 years [24].

2.3. Sex Ratio

A female predominance was reported by several regional investigations, as the female to male ratios ranged from 2.8:1 in Iowa [25] to as high as 4.25:1 in Europe [29]. Moreover, 2 large epidemiological studies conducted in Japan in 1997 and 2003 presented the female to male ratio as 1.8:1 [13,14]. However, this was different from the figures in some Chinese studies, where this ratio was reported to be 1.15:1 and 1.3:1 in Nanjing and Taiwan, respectively [17,18]. In addition, Bao et al. [19] found a 1:1 sex ratio in a recent single-center epidemiological study in China. This suggests that sex factors in the clinical characteristics of MMD patients in China are different from those in Japan, South Korea, and other Asian countries, which may be related to differences among races, regions, and environments.

3. GENETICS

In addition to region-specific incidences, family history was found in 12.1% of MMD patients [14]. Identical twins have a higher rate of MMD co-prevalence, and the offspring of MMD patients are about 34 times more likely to develop MMD than the general population [30]. Some cases have been reported to have co-existing MMD and genetic diseases, such as Down syndrome, neurofibromatosis and Turner syndrome, were reported [31, 32]. Multiple systems and organs are involved in these genetic disorders and cerebrovascular diseases could be one of their complications. A retrospective analysis also revealed a significantly higher prevalence of other diseases, particularly type 1 diabetes mellitus, hyperlipidemia, and thyroid disease, among MMD patients [33]. Taken together, genetic factors appear to play an important role in the pathogenesis of MMD.

An investigation of 16 Japanese families with MMD (total: 77 patients) in 1999 reported 3p24.2-26 as an early genetic locus associated with MMD [34]. This locus was also found in a study in a Greek twin-pair with MMD by Zafeiriou et al. [35] in 2003. Several other genetic loci were demonstrated to be related to Japanese familial MMD, i.e., 6q25, 8q23, 12p12, and 17q25 [36-38]. Notably, a rare 17q25 allele was much more frequent in Asian populations (Japanese, Korean, and Chinese), but was not detected in Caucasian cases [39]. The association of human leukocyte antigen (HLA) with various diseases also sparked some genetic investigations into MMD. For instance, significant association of HLA-DQB1*0502 [40], HLA-B51, and HLA-DR4 [41] was found with MMD in the Japanese population, and of HLA-DRB1(*)1302, HLA-DRB1(*)0609 [42], and HLA-B35 [43] with MMD in Korean patients. Moreover, the frequencies of HLA-DRB1*03, HLA-DRB1*13, HLA-A*02, HLA-B*08, and HLA-DQB1*03 were increased in
Caucasian MMD patients [44]. Other studies mainly focused on gene polymorphism of the tissue inhibitor of metalloproteinase (TIMP) [45], the vascular smooth muscle cell (SMC)-specific isoform of alpha-actin (ACTA2) [46], and ring-finger protein 213 (RNF213) [47, 48]. Mutations in RNF213, a zinc ring-finger protein that is related to intracranial major artery stenosis/occlusion [49], may affect the expression of some micro-RNAs and proteins associated with signaling processes involved in angiogenesis and immune activities that underlie the pathology and progression of MMD [50]. The amino acid substitution p.R4859K, the first identified RNF213 polymorphism associated with MMD, was found in 95% of patients with familial MMD, 80% of those with sporadic MMD, and 1.8% of control individuals in a Japanese population, in a genome-wide linkage and exome analysis study [51]. Other studies revealed the predictive role of this variant on the age of onset and Posterior Cerebral Artery (PCA) involvement in MMD cases [52]. In addition, several other variants in RNF213 were identified among Caucasian cases, namely p.N3962D, p.D4013N, p.R4062Q, and p.P4608S [53]. Additional mutations tended to be associated with ischemic- or hemorrhagic-type MMD in specific populations [54] and require further investigation.

4. PATHOPHYSIOLOGY

4.1. Immunity and Inflammation

In 1993, an autopsy conducted by Masuda et al. on 6 MMD patients revealed infiltration of macrophages and T cells in the thickened intima of the arteries in the circle of Willis composed predominantly of smooth muscle cells [55]. This provided insight into the participation of the immune system and inflammation in the pathophysiology of MMD [56]. Chronic inflammation may damage the vessel wall and cause microthrombi, leading to ischemic stroke. Moreover, the pro-inflammatory environment formed by the abnormal secretion of cytokines may also stimulate activation of endothelial cells and macrophages [57, 58], the proliferation of smooth muscle cells [59, 60], and neovascularization [61]. One investigation has found the higher expression of an M2 macrophage marker-sCD163 in the serum of MMD patients, indicating the possible role of macrophage in the progression of MMD. Transforming Growth Factor-β (TGF-β) is among these pro-inflammatory cytokines, capable of regulating various cell functions, such as proliferation, differentiation, and migration [62]. Peripheral TGF-β was found to be increased in MMD patients and showed a positive correlation with Suzuki’s stage MMD [63]. Increased expression of TGF-β could induce substantial extracellular matrix production, accompanied by intimal and medial hyperplasia in normal porcine arteries [64]. Similarly, higher serum levels of IL-1β, TNF-α, and IL-12 were also found in MMD patients than in age- and sex-matched healthy individuals; these levels also correlated with those detected in the cerebrospinal fluid (CSF) of these subjects [65].

Coexistence of MMD and some autoimmune diseases, such as type 1 diabetes mellitus [66], Graves’ disease [67], or thrombocytopenia [68] also urged investigation into the mechanism of immune regulation disorder and abnormal expression of immune proteins in the progression of MMD. Yanagawa et al. [69] reported an MMD case with positive findings for rheumatoid factor and myeloperoxidase-antineutrophil cytoplasmic antibody. Protein array data analysis followed by bioinformatics analysis has helped to identify 165 significantly overexpressed autoantibodies in sera from MMD patients, which were associated with post-translational...
modification, inflammatory responses, and DNA damage repair and maintenance [70]. Moreover, the deposition of IgG and IgM was found under the internal elastic lamina of the internal carotid artery and the anterior and middle cerebral arteries in 15 human autopsies of MMD cases [71]. The deposition of immune complexes may cause degeneration, tortuosity, and rupture of the inner elastic layer of the main cerebral vessels and their branches and can cause mass migration of the smooth muscle cells of the middle membrane to the subintima, leading to intima thickening and vascular lumen narrowing.

4.2. Endothelial Progenitor Cells

With the potential of differentiating into mature vascular endothelial cells, Endothelial Progenitor Cells (EPCs) participate in post-natal angiogenesis events, such as tumor angiogenesis [72] and vasculogenesis [73], within ischemic tissues [74], as well as in the maintenance of vascular homeostasis [75], in addition to embryonic vascular development [76]. Higher levels of circulating EPCs were found in MMD patients than in patients with atherosclerotic cerebrovascular disease and in healthy controls [77]. Moreover, this was observed in patients with angiographic moyamoya vessels, but not in patients with major cerebral artery occlusion (or severe stenosis) who did not have moyamoya vessels [78]. A prospective clinical trial also found a significant correlation between EPC count and good post-operative collateral circulation in 116 MMD patients [79]. However, seemingly contradicting reports found decreased levels of blood EPCs in a group of adult Caucasian MMD patients who had not undergone surgery [80] and in a group of children with MMD [81].

In addition to quantitative anomalies, the functional abnormality of EPCs may also play a role in the progression of MMD [81, 82]. This phenomenon exists due to a lack of standardized protocols for isolation, cultivation and identification of these cells, as different investigations were conducted using various techniques and with non-unified cell surface markers, concentrating on different subgroups of EPCs [82]. Early EPCs possess 3 specific surface markers: CD34, CD133, and vascular endothelial growth factor receptor 2 (VEGFR-2) [83], while late EPCs only express 2 markers: CD34 and VEGFR-2 [84]. EPCs at various stages could play different roles in the pathophysiology of MMD.

4.3. Nitric Oxide and Angiogenesis Related Cytokines

Nitric Oxide (NO), by binding to its only known receptor, guanylate cyclase (sGC) [85], plays an important biochemical role as a neurotransmitter and second messenger that is involved in various physiological and pathophysiological activities, including vascular smooth muscle remodeling [86] and vasoconstriction regulation [87], through an NO–sGC–cyclic guanosine monophosphate (cGMP) pathway [88]. This was confirmed by the dilatory effect of L-arginine, a precursor of NO, on murine cerebral arterioles and the contraceptive effect of N(G)-monomethyl-L-arginine (L-NMMA), an NO synthesis inhibitor [89]. Additionally, the level of NO in the CSF obtained from 23 MMD patients was significantly higher than that of control specimens from 16 non-MMD patients [89]. Additionally, disrupted NO signaling due to sGC mutation could lead to MMD [90, 91]. It could be speculated that changes in NO levels can influence vascular smooth muscle and promote the formation of abnormal vascular networks in the skull base, by expanding small vessels in the collateral circulation; however, the specific underlying mechanisms remain to be elucidated. In addition, caveolin-1 (Cav-1), a repressive modulator of NO, was found reduced in MMD patients and further in vitro study showed that Cav-1 downregulation suppressed angiogenesis in the endothelial cells and induced the smooth muscle cells apoptosis, indicating its negative role in arterial remodeling in MMD.

MMD patients exhibit significantly altered plasma concentrations of cytokines, including growth factors like Vascular Endothelial Growth Factor (VEGF), platelet-derived growth factor BB (PDGF-BB) [92] and angiogenesis related cytokines. The expression of VEGF [93] could be induced by hypoxia [94]. It is currently considered to be the most effective pro-angiogenesis growth factor. Significantly higher plasma concentration of VEGF was found in MMD patients.

During the progression of MMD, local cerebral hypoxia could give rise to changes in the expression of VEGF, which may contribute to the formation of moyamoya vessels. In addition, receptors responsible for VEGF-soluble VEGF receptor-1 (sVEGFR-1) and sVEGFR-2 were found to be reduced in MMD patients and MMD patients who underwent indirect bypass surgery tended to have better collateral formation with lower sVEGFR-1 and sVEGFR-2 levels. As a kind of angiogenesis related cytokines and targeting at collagen IV, matrix metalloproteinase-9 (MMP-9) causes endothelial basal lamina destabilization by degrading cell-cell and cell-matrix contacts and may participate in the disruption of the blood–brain barrier [92]. Sporadic studies have reported elevated expression of some other cytokines like basic Fibroblast Growth Factor (bFGF), Hepatocyte Growth Factor (HGF), and Platelet-Derived Growth Factor (PDGF-BB) and Monocytes Chemoattractant Protein-1 (MCP-1) in MMD patients’ serum or cerebrospinal fluid [95]. These cytokines mainly cause the proliferation of endothelial cells and migration of smooth muscle cells, leading to intima hyperplasia and pathological collateral vessel formation. However, whether these cytokines play initiating roles or are simply intermediate products during the progression of MMD remains unknown and deserves further investigation.

5. NEUROIMAGING EVALUATIONS

5.1. Digital Subtraction Angiography

MMD was first named as such in 1969 by Suzuki and Takaku because the appearance of this angiopathy on angiography is reminiscent of a puff of smoke (the meaning of “moyamoya” in Japanese) [96]. Digital subtraction angiography (DSA) is always the criterion standard for diagnosis of MMD [97]. DSA can not only evaluate the severity of stenosis in the terminal part of the internal carotid artery, but can also assess the degree of compensation from the external carotid artery and posterior circulation [98, 99]. Bonasia et al. [100] described the compensatory vascular systems in MMD and found 3 different types of anastomoses with different compensatory abilities, resulting from various perfusion needs of the anterior circulation. Recent studies based on DSA have mainly focused on the prediction of clinical
outcomes and prognosis in MMD [101-103]. Funaki et al. [104] demonstrated that choroidal anastomosis and posterior cerebral artery involvement are characteristic of intracranial hemorrhage in MMD, and might be risk factors for hemorrhagic MMD. Yamamoto and Hori et al. [105, 106] suggested that the longitudinal shift in collateral channels from the anterior to the posterior component might be closely related to the onset of hemorrhagic stroke in MMD, and may also be associated with ethnic differences. Zhang et al. [107] also found that direct anastomoses of the parasympathetic cortical arteries with anterograde hemodynamic sources from the middle cerebral artery had a high risk of postoperative complications in MMD. Notably, the literature has increasingly confirmed the value of DSA in the assessment of MMD [108], as it allows evaluation of hemodynamic characteristics and compensation [109], and possibly prediction of clinical outcomes [110]. However, a shortcoming of this method is that it cannot truly reflect the perfusion status of the brain parenchyma. Moreover, with increased understanding of DSA, the modified Suzuki grading system may facilitate risk stratification and prognosis prediction in patients with MMD [111].

5.2. Magnetic Resonance Imaging

There is no doubt that with advances in Magnetic Resonance Imaging (MRI) and development of different sequences, marked progress has been made in the understanding of MMD [112, 113]. Previous studies have suggested that different sequences of structural MRI (sMRI) can contribute to the objective evidence of MMD [114-116], showing gray matter atrophy and white matter deterioration with high spatial resolution [117]. Kazumata et al. [118] reported that the combination of diffusion tensor imaging and sMRI is potentially useful for tracking subtle anatomical changes, even though hemodynamic compensation may mask ischemic status in advanced stages of MMD. In addition, Susceptibility-Weighted Imaging (SWI) and time-of-flight magnetic resonance angiography (TOF-MRA) allows highly reproducible detection of the bleeding point in hemorrhagic MMD, which is a prognostic factor for rebleeding and assessing the degree of preventive effects [119, 120]. High-resolution vessel wall imaging also has potential utility for diagnosis as well as for indicating disease activity with the presence of wall thickening and enhancement in MMD [121, 122].

Functional MRI (fMRI) provides the opportunity to understand the functional connectivity between brain regions at neural, regional, and network levels [123]. Blood Oxygen Level Dependence (BOLD) is an emerging technique for the assessment of cerebrovascular reactivity in MMD [124, 125]. It is a very promising tool for hemodynamic evaluation and holds potential for becoming a routine examination in the pre- and postoperative evaluation of MMD patients in the future [126, 127]. Working memory and performance speed scores are inversely correlated to the degree of disruption of the default mode network changes, and can be detected by using resting-state fMRI [128]. This suggests a possible relationship between higher cognitive function and orderliness of fundamental brain networks. Analysis of resting state networks may produce potential biomarkers for cognition in MMD [129]. Using fMRI, Lei et al. [130] clarified static and dynamic organizational principles behind network changes in MMD, which provided some new insights into the pathophysiology and treatment direction.

Furthermore, different types of perfusion sequence MRI can provide hemodynamic information and have recently become hot research topics for MMD [131, 132]. Lin et al. [133] developed standardized Time-to-Peak maps and a scoring system via perfusion-weighted MRI to evaluate longitudinal perfusion changes in MMD and confirmed the predictive value of preoperative perfusion status. Arterial spin Labeling (ASL) is another MR perfusion method that relies on endogenous water molecules for signal and is increasingly used for quantitative cerebral blood flow measures in MMD [97, 113, 134]. Lee et al. [135] determined that ASL could be used as a noninvasive monitoring tool to identify perfusion changes, including cerebral blood flow, collateral blood flow, and anastomosis site patency after revascularization in MMD patients. Numerous modified methods [136, 137], such as velocity-selective ASL, offer a powerful approach to cerebral perfusion imaging with high accuracy, which holds marked research prospects for MMD.

5.3. Advanced Neuroimaging

Cerebral hemodynamic imaging, such as single-photon emission computed tomography, can evaluate the level of blood perfusion, and detects misery perfusion with high sensitivity in MMD [138, 139]. Positron-Emission computed Tomography (PET) seems to be more sensitive in detecting cerebral perfusion reserves, such as the Oxygen Extraction Fraction (OEF) and cerebrovascular reserve capacity, to clarify the mechanism of cognitive impairment for MMD [140-142]. Hara et al. [143] found that chronic ischemia in patients with MMD may induce decreased neurite and axonal density and simplified network complexity, which may lead to neurocognitive dysfunction. Lee et al. [144] also confirmed that severe hemodynamic impairment, indicated by increased OEF ratios on PET is associated with decreased cortical thickness in MMD. More importantly, hemodynamic evaluation is essential for MMD, to clarify vascular territories at risk of stroke [145, 146]. A previous study [127] found that the incidence of ischemic events was low and that cognitive function was stable in MMD without cerebral misery perfusion, which strengthened the surgical indications and concepts for MMD [147].

Electroencephalogram (EEG) can reflect the overall electrophysiological effects and the function of the brain network [148]. It is a noninvasive method with high temporal resolution that can reflect neuronal activities in patients with MMD [149]. A previous study has confirmed that EEG is useful for evaluating transient neurological events in MMD to distinguish seizures and epileptiform changes [150]. Additionally, postoperative transient neurological dysfunction resulting from transient cortical depression often occurs in MMD [151]. This can be detected by EEG, as low amplitude arrhythmic slowing in the corresponding hemisphere [152]. Some studies [153, 154] have also found that focal ischemic events as well as epileptic waves monitored on EEG correlated with clinical outcomes in MMD. Electrocorticography (ECoG) is another method for evaluating suppression of neurophysiologic activity and comparing spectral power.
Table 1. Different grading systems for moyamoya disease based on different neuroimaging methods.

| Year | Author          | Basis for Grading               | Objective                                                                 | Significance                                                                 |
|------|-----------------|---------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| 2011 | Czabanka, et al.| DSA, MRI & CVRC                 | Degree of stenosis of intracranial artery & compensation, Sign of ischemia, CVRC | Such system can stratify for clinical symptomatology                           |
| 2014 | Hung, et al.    | Color-coded parametric quantitative DSA, DSC-PWI | Delay time of maximal opacification between ICA and MCA                   | Such system correlates with angioarchitecture and hemodynamic impairment status |
| 2015 | Sahoo, et al.   | Angiographic outcome score       | Reformation of distal MCA and ACA, Regression of basal moyamoya vessels, Leptomeningeal collaterals and overall perfusion | Such score can reflect angiographic changes after revascularization             |
| 2017 | Ladner, et al.  | Prior infarcts, reactivity & angiography | DSA, Structural and hemodynamic MRI                                       | Such system correlates with symptomatology to evaluate hemodynamic severity    |
| 2018 | Yin, et al.     | CT perfusion                     | Cerebral perfusion status                                                 | Such system can evaluate cerebral perfusion status and predict the efficacy of revascularization |
| 2019 | Zhi-Wen, et al. | Collateral circulation and Suzuki stage | Anatomic extent of blood flow of intracranial and pial perforator         | Such system correlates with clinical symptoms, hemodynamic status, and therapeutic prognosis which may facilitate risk stratification and prognosis predictions in MMD patients |
| 2019 | Lin, et al.     | MRI perfusion                    | Standardized TTP maps using cerebellar reference values                   | Preoperative perfusion status is the only predictor of indirect revascularization outcome |
| 2020 | Moinay, et al.  | Demographics, multimodal imaging Surgical revascularization types | Hyperlipidemia & smoking, Cerebral infarction on preoperative CT or MRI, Reduced regional CVRC | Such system reveals the importance of smoking and hyperlipidemia to predict clinical outcome |
| 2020 | Mario, et al.   | DSA, MRI & Xenon-CT              | Structural intracranial vessels criteria, Sign of ischemia/hemorrhage/atrophy, CVRC | Such system can stratify hemispheric symptomatology and predict stroke events |

(CVRC: Cerebrovascular Reserve Capacity; DSC-PWI: Dynamic Susceptibility Contrast Perfusion-Weighted Imaging; ICA: Internal Carotid Artery; MCA: Middle Cerebral Artery; ACA: Anterior Cerebral Artery; CT: Computer Tomography; MRI: Magnetic Resonance Imaging; TTP: Time To Peak)

between different regions in the surgical area, which may provide insight into the potential neuromodulatory role of revascularization surgery [155, 156].

5.4. Future Directions

Various types of neuroimaging modalities have different clinical significance in the diagnosis and evaluation of MMD [157]. DSA and sMRI may be more sensitive for distinguishing characteristic structural changes and yield a higher spatial resolution. ASL as well as EEG may have better temporal resolution and could be more suitable for individual application. On the other hand, BOLD and PET are superior in functional evaluation of the brain and provides some new insights into MMD. Moreover, it cannot be refuted that neuropsychological evaluation is also a valuable assessment, because cognitive impairment resulting from MMD can also be detected on functional neuroimaging, which is of great significance in identifying asymptomatic MMD and disease progression [158]. Multiple studies [130, 150] have found abnormalities on fMRI and EEG, which correlated strongly with cognitive changes and clinical manifestations. Investigation of the connection between cognitive status and advanced neuroimaging have become a focus in MMD, with marked potential [159]. Yet, each neuroimaging modality has its own limitations, which might be complemented by using multimodal image fusion techniques. The Berlin grading system [160] involves DSA, sMRI, and functional cerebrovascular assessment of hemodynamic impairment, and correlates with disease severity. More importantly, it allows stratification of the individual risks of surgical therapy. Although there are many types of staging systems for MMD, based on clinical characteristics and imaging findings (Table 1), an appropriate grading system for MMD that can clarify the true progression of the disease is still lacking.

6. TREATMENT

6.1. Medical Treatment

In terms of treating the common symptoms of MMD, the use of antiplatelet and many other agents focuses on symptomatic control [10, 161]. The results of a nationwide survey in Japan [162] showed that the selection of antiplatelet drugs
varied widely across facilities and there is no consensus treatment. Notably, some researches [163] showed that cilostazol improves cerebral perfusion as well as cognition better than other antiplatelet drugs for ischemic MMD patients. Meanwhile, a recent 10-year follow-up evaluation has demonstrated that the use of antiplatelet agents did not influence the rate of cerebral infarction in patients with MMD [163]. Treatment indications for asymptomatic MMD are currently being revisited in the AMORE trial [164]; more research evidence is needed to confirm the efficiency of conservative therapy with antiplatelet drugs [165]. Given the vascular cognitive impairment caused by MMD [114], acetylcholinesterase inhibitors, such as donepezil and rivastigmine, have generally been approved for modest cognitive benefits [166]. Moreover, butylphthalide may alleviate perioperative neurological deficits in cases with unfavorable preoperative status [167]. Taken together, effectiveness of medical treatment for MMD remains unclear and further investigations are urgently needed [168].

6.2. Revascularization

Surgical treatment is the most effective method to restore the blood supply and increase cerebral perfusion in order to prevent secondary stroke in ischemic MMD and to stabilize cerebrovascular hemodynamics to regress fragile moyamoya vessels to prevent bleeding in hemorrhagic MMD [11, 169], which then improves neurocognitive outcomes [170]. In surgical practice, endovascular treatment and revascularization are often applied; the latter includes indirect, direct, and combined revascularization [171].

6.2.1. Endovascular Treatment

Endovascular treatment (EVT) has become the current mainstream treatment for MMD-associated aneurysms [172]. Previous reports have shown that endovascular embolization is safe and efficacious for treating intracranial aneurysm with liquid embolic agents or coils in most locations in patients with MMD [173, 174]. Moreover, some studies [175, 176] have reported that while EVT can be applied in atherosclerotic moyamoya syndrome, it is a major challenge to perform EVT for MMD in stenosed arteries in which super-selective catheterization is technically difficult [177]. Indeed, there are plenty of attempts to treat MMD by EVT in order to improve forward blood flow of target vessels. Due to the pathogenesis of MMD being vasculitis-like angiopathy with concentric stenosis of intracranial artery, both angioplasty and stenting may promote inflammatory reaction in the artery, of which the long-term clinical outcomes remain controversial.

6.2.2. Direct Revascularization

Direct revascularization via anastomosis of the superficial temporal artery to the middle cerebral artery (STA-MCA bypass) has been the most common procedure for addressing the MCA territory [178], but also supports the anterior cerebral artery territory via leptomeningeal anastomoses [179, 180]. Particularly, Kurihara et al. [181] reported that the posterior auricular artery can also be used as the donor artery using a double direct bypass technique for cases with poor development of the STA. Multiple reports have confirmed that direct revascularization is more effective in preventing recurrent ischemic strokes for adult ischemic-type MMD [182, 183], while, direct bypass is challenging in children, where bypass patency rates have been reported to be lower [184, 185].

6.2.3. Indirect Revascularization

Indirect revascularization relies on neovascularization of the cortical surface using angiogenic mechanisms from pedicle-based grafts, such as pial synangiosis, and temporal muscle grafts, which are generally easier to perform [186, 187]. However, the hemodynamic protective effects may take months to develop and are not very predictable [188]. A previous study confirmed that indirect bypass surgery could provide satisfactory long-term improvement in overall clinical outcomes and prevention of recurrent stroke in children with MMD [189]. Another previous study proved that encephalo-duro-arterio-synangiosis was beneficial for patients with hemorrhagic MMD through long-term follow-up [190]. Mirone et al. [191] also emphasized the good success rate of using multiple burr holes in pediatric MMD, which could be an effective support to produce good collateral revascularization and improve cerebral perfusion. Such burr-hole surgery could provide satisfying clinical symptom control with low perioperative risk. In addition to the abovementioned coverage of the brain surface, other strategies, such as Encephalo-Duro-Myo-Synangiosis (EDMS) and omental transplantation have also been applied to stimulate transcranial angiogenesis [192]. There are a wide variety of indirect techniques, but which of these techniques is superior to the others remains unknown.

6.2.4. Combined Revascularization

Combined revascularization includes direct and indirect bypasses; the latter aims to achieve both immediate and later hemodynamic improvement and serves as a fallback strategy in case the direct bypass fails [193]. Multiple reports [194, 195] have confirmed that combined revascularization would be the best choice for preventing not only further ischemic events, but also hemorrhagic stroke, by improving anterior choroidal artery-posterior communicating artery dilation and extension. Additionally, Kazumata et al. [196] reported that combined revascularization may improve cognitive function, including processing speed and attention in MMD patients with evidence of postsurgical structural brain changes. However, we encountered a patient with intraventricular hemorrhage (IVH) who was diagnosed with MMD accompanied with a pseudoaneurysm in our center (Figs. 2A, 2B; white arrow), in whom combined revascularization was performed (Fig. 2C). Long-term angiographic follow-up showed good patency of the donor artery, satisfactory compensation from EDMS, and disappearance of the pseudoaneurysm (Figs. 2D-F). After 1 year, the patient suffered from headache and Computed Tomography (CT) showed IVH, as before, but showed no significant findings on DSA (Figs. 2G-I). SWI revealed multiple right paraventricular microbleeds (Fig. 2J; dotted arrow). It remains unclear what should be done for such patients, and how rebleeds should be prevented [173]. In addition, postoperative hyperperfusion syndrome, such as aphasia, epileptic seizures, and even new cerebral hemorrhage or ischemia, are experienced frequently in the acute phase after such combined revascularization processes, and these can progress to irreversible sequelae [197]. Therefore, appropriate methods with sufficient evidence are urgently needed.
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Fig. (2). This patient was found to have Intraventricular Hemorrhage (IVH) and was diagnosed with moyamoya disease accompanied with pseudoaneurysm (A, B, white arrow) at our center. Combined revascularization (superficial temporal artery to the middle cerebral artery bypass and encephalo-duro-myo-synangiosis) was performed (C). The 6-months follow-up with digital subtraction angiography (DSA) showed good compensation from the external carotid artery and disappearance of the pseudoaneurysm (D, E, F). After 1 year, the patient suffered from headache. IVH was found on computed tomography, but there was no significant finding on DSA (G, H, I). Susceptibility-weighted imaging was performed and revealed multiple right paraventricular microbleeds (J; dotted arrow). (A higher resolution/colour version of this figure is available in the electronic copy of the article).

Fig. (3). Evaluating methods, including Digital Subtraction Angiography (DSA), structural Magnetic Resonance Imaging (sMRI), Arterial Spin Labeling (ASL), positron emission tomography (PET), indocyanine green angiography (ICG-FLOW800) and electrocorticography (ECoG) can reflect different characteristics, such as angioarchitecture, cerebral perfusion, and metabolic status in different hemispheres from the perspective of structure to function. Such modified revascularization based on multimodal neuroimaging guidance aims to provide objective evidence for surgical decision-making and can decrease peri-operative complications of moyamoya disease. (A higher resolution/colour version of this figure is available in the electronic copy of the article).

6.3. Neurological Rehabilitation

Neurological rehabilitation also plays an important role in vascular cognitive impairment caused by MMD. Perng et al. [198], in their meta-analysis, found that systematic cognitive training is an effective intervention for MMD. Formica et al. [199] also found that specific motor and neuropsychological rehabilitative treatments provided advantages in the care of MMD patients with disorders of consciousness. In
particular, psychological intervention for pediatric MMD patients is important to improve post-operative quality of life and physical, emotional, social, and school functional outcomes [200]. Choi et al. [201] also confirmed the effectiveness of remote ischemic pre- and post-conditioning in reducing neurological complications and the duration of hospitalization in MMD patients undergoing STA-MCA anastomosis. Taken together, neuroprotection and neurorecovery enhancement have marked potential as MMD treatments. A standard neurological rehabilitation protocol needs to be established [202].

### 6.4. Future Directions

Although surgical revascularization is the most successful treatment for improving cerebral perfusion and reducing the risk of stroke events in MMD patients, the rate of complications, such as hyperperfusion syndrome, cerebral infarction, and epilepsy, remains very high due to hemodynamic abnormalities. Nevertheless, the distribution of global and regional perfusion, metabolism, as well as neuronal activity, are also important influencing factors in surgical decision-making regarding bypass surgeries [203]. Additionally, the choice of recipient vessel is currently based on the experience of the surgeon, without objective evidence. A modified method of operation is needed to reduce the incidence of complications [104]. With multi-dimensional neuroimaging evaluations of MMD, assessment that includes angiarchitectures, cerebral perfusion and metabolism, regional hemodynamic parameters, and neuronal activities by means of DSA, ASL, PET-CT, indocyanine green angiography (ICG-FLOW 800), and intraoperative electrocorticography [204]. With such evaluations, the ischemic as well as dysfunctional cortical area can be accurately confirmed so as to choose the appropriate recipient artery, and the clinical outcomes of bypass surgery may improve and the complication rate decrease (Fig. 3).

### CONCLUSION

Taken together, not only are the clinical features of MMD complicated, but the diagnostic criteria and treatment strategy for MMD need to be developed further. More nationwide studies are urgently needed to clarify the mechanism and risk factors of MMD and explore more efficient preventative measures. There are numerous neuroimaging methods that can be used to evaluate the progression of MMD, in terms of different aspects, which can also be useful in facilitating an appropriate bypass.

### AUTHORS’ CONTRIBUTION

XZ and WPX performed all data acquisition and interpretation, and drafted the manuscript. QZ assisted with data interpretation and revised the manuscript. DX and PG assisted with neuroimaging and helped to draft the manuscript. JBS, HY, and XJG assisted with data collection. WN, YL, and YXG guided article revision. All authors contributed to the article and approved the submitted version.

**CONSENT FOR PUBLICATION**

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### CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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