Pathophysiology of Moyamoya Disease

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Moyamoya disease is a chronic progressive steno-occlusive disease of the distal internal carotid artery or proximal anterior cerebral artery and the middle cerebral artery with abnormal moyamoya collateral vessels without associated diseases. The disease has been increasingly reported due to the technological advances of diagnostic radiology and an increase of health check-up. The studies regarding the incidence, prevalence, natural clinical course, disease progression, and surgical treatment outcomes have been increasingly reported. Nevertheless, the precise mechanism of the disease still remains to be investigated further. In addition, heterogeneity of the ethnicity, different age at presentation, different degrees of hemodynamic compromise, surgical techniques such as direct bypass or indirect bypass surgery, and relative small sample size could lead to controversial results. This chapter provides insights into the pathophysiology of the disease including histopathological features, genetics, Ring finger protein 213, microRNAs, molecular biomarkers, vascular progenitor cells, proteomics, metabolomics, and associated autoimmune diseases.

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2.1 Background

Moyamoya disease (MMD) is characterized by the chronic progressive steno-occlusive disease of the distal internal carotid artery (ICA) or proximal anterior cerebral artery (ACA) and the middle cerebral artery (MCA) with abnormal moyamoya vessels [1]. MMD has been highly reported in East Asia, in particular Japan and Korea. In Japan, the estimated prevalence has increased from 3,900 in 1994 to 7,700 cases in 2003 [2]. The crude prevalence rate in Korea also has increased from 6.6 in 2005 to 19.5 in 2013 [3]. MMD shows an approximately 2:1 female predominance and bimodal age pattern [4]. The disease progression of MMD has been reported ranging from 14.6% to 50% [5–7]. Although the patients were asymptomatic, the estimated annual stroke risk rate was 3.2% [8]. As such, MMD has a dynamic nature which requires surgical treatment.

In this chapter, we provide insights into the pathophysiology of the disease including histopathological features, genetics, Ring finger protein 213, MicroRNAs, molecular biomarkers, vascular progenitor cells, proteomics, metabolomics, and associated autoimmune diseases.

2.2 Histopathological Features

The main pathological changes are eccentric fibromuscular thickening of the intima due to abnormal proliferation of smooth muscle cell

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(SMC), thinned media, prominently tortuous internal elastic laminae, and a decreased outer diameter [9–11]. The moyamoya vessels have various histopathological changes such as thinned media, fibrin deposit in the arterial wall, fragmented elastic laminae, attenuated media, and microaneurysm [10–12]. Kaku et al. [13] showed narrowed arterial outer diameter of the ICA and MCA in MMD patients by three-dimensional interference in steady-state MR imaging. They suggested that constrictive remodeling of the affected arteries is a main phenomenon in MMD distinguishing from atherosclerotic stenosis.

2.3 Genetics

Genetic approach to understanding the MMD has been performed using candidate gene association studies including human leukocyte antigen (HLA) genotyping, genome-wide linkage analysis, and genome-wide association study (GWAS). Aoyagi et al. [14] found that HLA-B51-DR4 combination was increasingly noted in Japanese MMD patients. HLA-B35 allele was also significantly noted in Korean MMD patients, in particular female of late-onset MMD [15]. Hong et al. [16] suggested that HLA-DRB1(*)1302 and DQB1(*)0609 haplotype could be related to intimal fibrosis and arterial occlusion. Inoue et al. [17] reported that early-onset MMD showed increased DRB1(*)1501 and DQB1(*)0602. There are conflicting results concerning the association between tissue inhibitor of metalloproteinase (TIMP) genes and MMD. A G/C heterozygous genotype at position −418 of TIMP-2 promoter region was significantly observed in familial MMD [18]. They suggested that G/C heterozygous genotype at position −418 of TIMP-2 promoter region might be a genetic predisposing factor familial MMD through influencing Sp1 binding and subsequent TIMP-2 transcription. On the contrary, Paez et al. [19] did not find significant difference of heterozygous genotype at position −418 in MMD patients. In particular, only one familial MMD (1/7, 14.3%) showed G/C heterozygous genotype. Andreone et al. [20] also did not find the G/C heterozygous genotype in the promoter region of the TIMP-2 genes in monozygotic twins. For genome-wide linkage analysis, several loci such as 3p24–26 [21], 6q25 [22], 8q23, 12p12 [23], and 17q25 [24] were reported to be linked to MMD; however, 17q25 locus was only demonstrated in other series [10, 11].

2.4 Ring Finger Protein 213

A genome-wide linkage and association analyses revealed the Ring finger protein 213 (RNF213) as a susceptible gene for MMD [25, 26]. c.14576G>A (p.R4859K) RNF213 variants was frequently observed in familial MMD (95%) compared to nonfamilial MMD (73%) or control groups (1.4%). Liu et al. [26] also revealed an association between p.R4810K RNF213 variant and Asian MMD patients. Homozygous c.14576G>A RNF213 variant was noted in 95.1% of familial MMD, 79.2% of nonfamilial MMD, and 1.8% of control [27]. Homozygotes were associated with MMD of early onset and poor prognosis than heterozygotes and wild type [25, 27]. Wu et al. [28] reported p.R4810K RNF213 variant rate: familial MMD (n = 4, 80%), nonfamilial MMD (n = 18, 10.9%), and control group (n = 2, 0.39%) in Chinese population. When it comes to clinical presentations, ischemic presenting MMD was associated with p.R4810K variant and hemorrhage presenting MMD was non-p.R4810K variant, more specifically A4399T in Chinese MMD patients [11, 28]. Regarding Korean MMD patients, early-onset MMD (<5 years) and cerebral infarction were related to the homozygous c.14429G>A (p.R4810K) variant [29]. Nevertheless, p.R4810K variant could be more susceptible to East Asian MMD patients. Cecchi et al. [30] found that p.R4810K variant was observed in 56% in 16 MMD patients of Asian descent and 0% in 94 MMD of non-Asian descent in the United States.

Wang et al. [31] evaluated interaction effect on MMD development among PDGFRB (platelet-derived growth factor receptor beta) (rs3828610), MMP-3 (matrix metalloproteinase) (rs3025058), TIMP-2 (tissue inhibitors of metalloproteinase) (rs8179090), and RNF213 (rs112735431 and rs148731719) in Chinese population. They reported that RNF213 may have a

remarkable effect on MMD development; however, three remaining loci were not related to MMD significantly. Accordingly, such five gene polymorphisms could not have distinctive interaction effect on MMD in Chinese population. Nevertheless, the exact mechanism of RNF213 polymorphism remains unknown in MMD occurrence. RNF213 knockdown zebrafish showed irregular arterial wall and abnormal sprouting vessel, although mutant alleles did not affect transcription or ubiquitin ligase activity [26]. However, mice lacking the RNF213 gene [32] or mice with the R4859K mutation of RNF213 gene [33] did not show typical vasculature of MMD. Accordingly, further studies on the role of RNF213 in MMD pathogenesis and its association with MMD phenotypes are required.

2.5 MicroRNAs

MicroRNAs (miRNAs), small noncoding RNAs which regulate gene expression at the posttranscription level by binding to the 3′-untranslated regions of specific miRNAs [34], have been reported to be related to ischemic stroke [35]. Liu et al. [35] reported that miRNA-424 had a protective effect to the cerebral ischemia-reperfusion injury by inhibiting oxidative stress. A genome-wide miRNA analysis [34] showed that miRNA-106b, miRNA-130a, miRNA-126, and miRNA125a-3p were associated with MMD development by inhibiting RNF213 and BRCC3 protein expression which led to defective angiogenesis. Park et al. [36] reported that GT+CC genotype of the SNP rs11614913 in miR-196a2C>T was increasingly observed in MMD patients. Consequently, the role of serum miRNAs in MMD pathogenesis requires further study focusing on therapeutic target.

2.6 Molecular Biomarkers

Arteriogenesis and vasculogenesis are main topics for MMD research. Various enzymes, growth factors, adhesion molecules, and inflammation in the arterial remodeling pathway have been investigated (Table 2.1) [49]. MMD patients showed higher level of matrix metalloproteinases (MMP)-9,

Table 2.1 Relevant studies for Moyamoya disease (MMD) biomarker

Reference	Country	No*	Samples	Main findings
Takahashi et al. [37]	JPN	15	CSF	bFGF ↑
Houkin et al. [38]	JPN	48	CSF	bFGF ↑ in bilateral MMD
Yoshimoto et al. [39]	JPN	38	CSF	bFGF ↑
Malek et al. [40]	USA	37	CSF	bFGF ↑
Hojo et al. [41]	JPN	20	Serum and STA culture	TGF ß-1↑
Soriano et al. [42]	USA	20	CSF and serum	VCAM-1, ICAM-1, E-selectin ↑ in CSF, not serum level
Kim et al. [43]	KOR	20	CSF	CRABP-1↑
Amano et al. [44]	JPN	29	Serum	α1-antitrypsin ↑
Nanba et al. [45]	JPN	39	CSF	HGF↑
Kang et al. [46]	KOR	20	Plasma	VEGF, PDGF BB, MMP-9, MCP-1, IL-1ß↑/ MMP-3, TIMP-1,2↓
Bernard et al. [47]	USA	7	Serum	D-dimer ↑in MMD and cardioembolic ischemic stroke
Jeon et al. [48]	KOR	77	CSF	CRABP-1↑in bilateral MMD in relation to decrease in basal collateral vessels

No*: number of enrolled MMD patients

bFGF basic fibroblast growth factor, *CRABP-I* cellular retinoid acid-binding protein-I, *CSF* cerebrospinal fluid, *E-selectin* endothelial selectin, *HGF* hepatocyte growth factor, *ICAM-1* intercellular adhesion molecule 1, *IL-1ß* interleukins-1ß, *MCP-1* monocyte chemoattractant protein-1, *MMP* matrix metalloproteinases, *PDGF-BB* platelet-derived growth factor BB, *STA* superficial temporal artery, *TGF ß-1* transforming growth factors ß-1, *TIMP* tissue inhibitor of metalloproteinase, *VCAM-1* vascular cell adhesion molecule 1, *VEGF* vascular endothelial growth factor

monocyte chemoattractant protein-1 (MCP-1), interleukins (IL)-1ß, vascular endothelial growth factor (VEGF) and platelet-derived growth factor BB (PDGF-BB), and lower level of TIMP-1 and TIMP-2 compared to controls [46]. Johnson et al. [50] reported that MMP-9 genetic deficiency resulted in decreased formation of intimal hyperplasia and SMC attachment to gelatin. Accordingly, disruption of balance between MMP and TIMP which is an inhibitor for MMP could lead to intimal hyperplasia through excessive SMC migration and proliferation [46]. MCP1 is related to initiation of arteriogenesis [51]. And VEGF to endothelial progenitor cells (EPCs) mobilize under ischemic condition [52]. Consequently, both MCP1 and VEGF could be related to the recruitment of vascular progenitor cells and subsequent MMD vessel formation [46]. Hepatocyte growth factor (HGF) [45] and transforming growth factors ß-1 [41] were also increased in MMD patients. Nevertheless, it remains unclear if inflammatory proteins are specific to MMD itself, not reflecting cerebral ischemic condition (Fig. 2.1).

Retinoid signaling pathway was reported to be related to MMD pathogenesis. Higher level of cellular retinoid acid-binding protein-I (CRABP-I) was noted in both pediatric [43] and adult MMD patients [48]. They hypothesized that CRABP-I inhibited the retinoid activity which resulted in neointimal thickening by enhancing

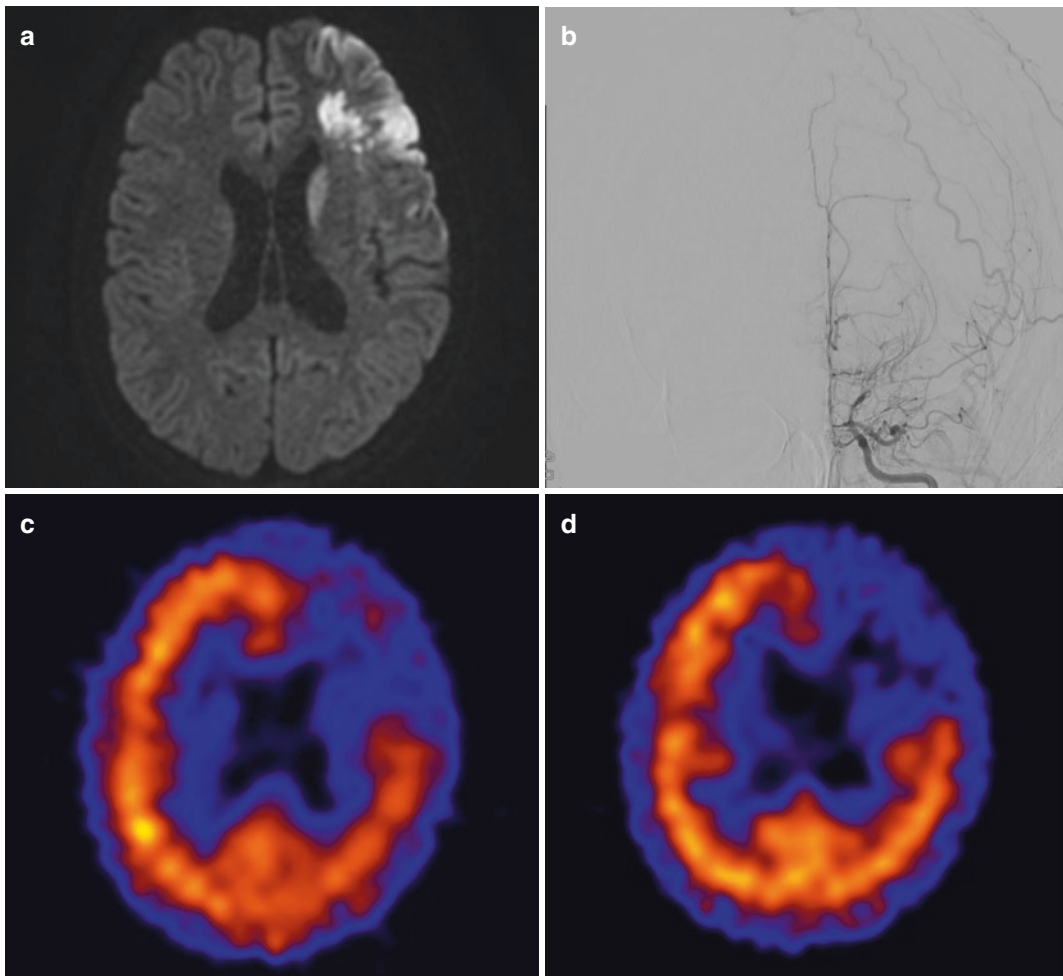

Fig. 2.1 A 30-year-old female presented with sudden onset right side weakness and dysarthria. Diffusion MR revealed acute infarction at Lt. Frontal anterior border zone (**a**). Angiography disclosed nearly total occlusion of the distal ICA occlusion on the left side (**b**). Single-photon emission computed tomography (SPECT) showed perfusion defect in the left frontal area with decreased basal perfusion in the resting state and decreased vascular reserve capacity in the acetazolamide challenge test (**c** and **d**).

growth factors. In particular, for adults, increased CRABP-I was related to typical bilateral MMD [48]. In addition, higher CRABP-I was related to a decrease in basal collateral vessel after bypass surgery. Accordingly, studies of retinoids as a therapeutic target for MMD are needed further.

2.7 Vascular Progenitor Cells

Circulating EPCs have been suggested as a pathogenic marker for MMD. Sugiyama et al. [53] directly stain the specimens of the distal ICA using antibodies of CD34, CD133, and vascular endothelial growth factor receptor-2 (VEGFR2) to localize the circulating EPCs in two adult MMD patients. Histopathological analyses showed that CD34− and VEGFR2+ cells were widely found in the thickened intima of the specimen. Nevertheless, the role of EPCS in MMD pathogenesis remains controversial. Jung et al. [54] reported that MMD patients revealed markedly decreased colony-forming unit (CFU) numbers on 7-day culture and elevated outgrowth cells during 2-month culture than control group. Similarly, decreased level of CD34+, CD133+, and KDR+ cells were noted in pediatric MMD, which were related to less tube formation and increased senescent-like phenotype [55]. Deregulation of retinaldehyde dehydrogenase 2 (RALDH2) of endothelial colony-forming cell was related to defective angiogenesis in pediatric MMD patients [56]. On the contrary, higher level of circulating EPCS was demonstrated in MMD patients [52]. Yoshihara et al. [57] found increased CD34+ cells which could attribute to neovascularization at sites of ischemic injury in MMD patients [57]. Ni et al. [58] also suggested that increased level of circulating CD34+, CXCR4+, and SDF-1α were related to MMD vasculogenesis. Heterogeneity of the ethnics, patients' age, and experimental methods could lead to controversial results among the studies; therefore, further researches are required to yield the EPCs' role in MMD pathogenesis [10].

MMD is characterized by the proliferation of SMC in the affected arteries. Accordingly, isolation of specific smooth muscle progenitor cells (SPCs) and its differentially expressed genes (DEG) analyses can be a dynamic model for MMD research [49]. Kang et al. [59] purified SPCs from peripheral blood in MMD patients (n = 25) and investigated DEGs. The SPC outgrowth cells in MMD patients revealed higher expression of alpha-smooth muscle actin, myosin heavy chain and calponin, and lower expression of CD 31 with more irregular and thickened tubules of SPCs than healthy control group. DEG analyses also showed increased expressed gene related to cell adhesion, cell migration, immune response, and vascular development in MMD SPCs. Further studies to identify relationship to specific change of SPCs in MMD pathogenesis are needed [60].

2.8 Recent Proteomic and Metabolomic Analyses

Two studies for identifying CSF biomarkers have been published using surface-enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF-MS) and metabolomics [61, 62]. Maruwaka et al. [61] reported increased three peptides of 4,473 Da, 4,475 Da, and 6,253 Da in 20 MMD patients (11 pediatric and 9 adult cases) by SELDI-TOF-MS. In particular, 4,473 Da peptide showed high correlation to postoperative angiogenesis and higher peak in younger MMD patients. Although precise role of 4,473 Da peptide remains unclear, they thought that 4,473 Da peptide could be related to anti-hypoxic effect or inflammation degree in MMD pathogenesis [61]. Jeon et al. [62] compared the CSF metabolites of adult bilateral MMD than those of unilateral MMD and atherosclerosis using a hydrogen-1 nuclear magnetic resonance spectroscopy. Bilateral MMD revealed higher level of glutamine than atherosclerotic stenosis. Considering the association between increased glutamine and intima-media thickness of the carotid and coronary artery disease [63], they postulated that increased glutamine in MMD could be related to more an abnormal SMC proliferation and intima thickness than atherosclerotic stenotic disease, although precise mechanisms is not well understood [62].

2.9 MMD in Association with Thyroid Disease

Several studies have illustrated MMD and concurrent autoimmune diseases, in particular thyroid diseases [64–66]. T-cell dysregulation [64] or increased sensitivity to the sympathetic nervous system of the vessel [65] has been suggested as pathomechanisms of the abnormal SMC proliferation and collateral vessel formation in MMD. Kim et al. [66] found that thyroid autoantibodies were significantly increased in MMD patients. They postulated that immune aberrancies related to thyroid autoimmunity may have a role in MMD pathogenesis. Recently, Chen et al. [67] reported that overall autoimmune diseases were significantly highly observed in unilateral MMD than bilateral MMD. Nevertheless, the actual pathogenic mechanisms of the autoimmune diseases in the development of MMD are still poorly understood. Accordingly, studies about autoimmune mechanism in MMD development, in particular the role of elevated thyroid autoantibodies in MMD development and progression, and its therapeutic target, are needed further [66, 68].

Conclusion

Although a better understanding of MMD has been achieved, the pathophysiology of MMD still remains fully understood. Heterogeneity of the ethnicity, patient age at presentation, and small sample size could lead to controversial results. Accordingly, high-throughput technologies in the effective biomarker for MMD, in particular disease severity or treatment outcomes in more homogeneous condition, are necessary.

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