Moyamoya disease: a review of histopathology, biochemistry, and genetics

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Object. Moyamoya disease (MMD) is a rare cerebrovascular disorder involving stenosis of the major vessels of the circle of Willis and proximal portions of its principal branches. Despite concerted investigation, the pathophysiology of the disorder has not been fully elucidated. Currently, the major proteins believed to play an active role in the pathogenesis include vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), transforming growth factor-β (TGFβ), and granulocyte colony-stimulating factor (G-CSF). In terms of the genetics, recent literature suggests a low penetrance autosomal dominant or polygenic mode of transmission involving chromosomes 3, 6, 8, 12, and 17 for familial MMD. This review summarizes the current knowledge on the histopathology, pathophysiology and genetics of MMD.

Methods. A PubMed/Medline systematic study of the literature was performed, from which 45 articles regarding MMD pathophysiology were identified and analyzed.

Conclusions. Moyamoya disease is characterized by the intimal thickening and media attenuation of the proximal vessels of the circle of Willis as well as the development of an aberrant distal vascular network. The primary proteins that are currently implicated in the pathophysiology of MMD include VEGF, bFGF, HGF, TGFβ, and G-CSF. Furthermore, the current literature on familial MMD has pointed to a low penetrance autosomal dominant or polygenic mode of transmittance at loci on chromosomes 3, 6, 8, 12, and 17. (DOI: 10.3171/2011.3.FOCUS1151)

Key Words • moyamoya disease • histopathology • biochemistry • genetics

Initially defined in 1969 by Suzuki and Takaku,11 moyamoya disease is an uncommon, progressive cerebrovascular disease involving spontaneous occlusion of the vessels of the circle of Willis and its principal branches, with a predilection for the internal carotid arteries.7 The generally bilateral stenosis coincides with the development of an aberrant network of collateral circulation vessels that leads to hemorrhagic and ischemic strokes. The term “moyamoya” in Japanese means a “hazy puff of smoke,” in reference to the characteristic appearance of the collateral vessels on cerebral angiography (Fig. 1).

While MMD is most prevalent in Japan, its presence has been reported in various populations around the world.1 The disease still appears to be more prevalent in east Asian countries including inland China, which has had an increasing incidence over the past decade.23 A national study in Japan has reported the incidence of MMD to be 0.35 per 100,000,37 whereas an analysis of the western US identified a significantly lower incidence of 0.086 per 100,000.35 Potentially indicative of a genetic component, Asian-Americans in the western US were affected on the order of 0.28 per 100,000, an incidence much more comparable to the Japanese incidence.35 Also, prevalence in females is slightly higher than that in males with a ratio of 1.8:1.3

Moyamoya disease can be organized as follows: ischemic, hemorrhagic, epileptic, and other;6 however, no specific pathophysiological distinctions have been established between these presentation categories. More commonly the disease is organized into adult and pediatric subtypes. Children are more likely to suffer from ischemia, while adults do not have a specific predilection for ischemic or hemorrhagic complications.9,13,19 Furthermore, pediatric patients suffer significantly greater cognitive impairment.17 This review includes a discussion of the pathophysiology of MMD with an emphasis on the current understanding of potential angiogenic agents and underlying genetic factors contributing to MMD presentation.

Abbreviations used in this paper: bFGF = basic fibroblast growth factor; G-CSF = granulocyte colony-stimulating factor; HGF = hepatocyte growth factor; MLS = maximum log 10 odds (LOD) score; MMD = moyamoya disease; MMP = matrix metalloproteinase; TGF = transforming growth factor; VEGF = vascular endothelial growth factor.
Methods

For this review, a systematic search of the English-language literature was performed with the PubMed/Medline database using the key words and various combinations of the key words: “moyamoya disease,” “pathology,” “genetics,” and “angiogenic proteins.” This search initially retrieved 112 articles, the abstracts of which were independently reviewed by 2 authors (D.G.W. and O.M.A.) for relevance to the topics of moyamoya pathophysiology or genetics. Reference lists of the relevant articles were reviewed for additional sources, and 43 articles were included in the final review.

Results and Discussion

Although the exact pathophysiology of MMD is yet to be fully elucidated, there have been several recent strides toward that goal. We reviewed the histopathology of the disease, and follow this by a discussion of suspect contributory angiogenic factors and their genetic underpinnings.

Histopathology

The large vessels of the circle of Willis, in the setting of MMD, typically display fibrocellular thickening of the tunica intima with excessive proliferation of the vascular smooth-muscle cells, marked tortuosity of the internal elastic lamina, and attenuation of the tunica media (Fig. 2).

The distal collateral vascular networks that are characteristic of MMD, however, commonly demonstrate an irregular-shaped lumen with either intimal wall thickening or thinning consistent with the angiographic appearance of abnormal angioarchitecture (Fig. 3).

Biochemistry and Angiogenic Factors

As a response to both hypoxia and decreased blood flow, angiogenic agents are generated in supraphysiologic concentrations (Table 1). These proteins induce the revascularization of the distal hypoperfused regions by forming the fragile collateral moyamoya vessels, which are implicated in the hemorrhagic presentations of MMD.

The potential impact of intraarterial microthrombi in the stenotic vasculature of MMD has been a point of contention. In their series, Yamashita et al. noted the presence of thrombi in 16 of 22 patients with MMD and concluded that the thrombi were closely related to the development of a thickened intima in the intracranial arteries. They attributed this pathological development to the thrombotic components, such as platelets and plasma constituents. Furthermore, Bonduel and colleagues presented evidence relating pediatric MMD to prothrombotic disorders including inherited protein S deficiency, lupus anticoagulant, and anticardiolipin antibodies in MMD. Masuda et al. however, found microthrombi to be absent in 5 of 6 patients. Furthermore, they noted the infiltration of macrophages and T cells in nonstenosed areas of the vessels, and they suggested that the microthrombi may be a result of the chronic inflammation rather than

![Fig. 1. Anteroposterior (left) and lateral (right) digital subtraction angiograms of the left internal carotid artery demonstrating the characteristic collateral vessels of MMD.](image1)

![Fig. 2. Microscopic findings in the left middle cerebral artery showing obstruction of the lumen, fibrocellular intimal thickening, marked tortuosity of the internal elastic lamina, and attenuation of media. Elastica H & E, original magnification x 40. Reprinted from Takekawa et al: Pathological and immunohistochemical findings of an autopsy case of adult moyamoya disease. Neuropathology 24:236–242, 2004, with permission from John Wiley and Sons.](image2)

![Fig. 3. Microscopic findings of peripheral portion of arteries in the left temporal lobe demonstrating dilated or irregular-shaped lumen and occasionally thickened intima. Elastica H & E, original magnification x 40. Reprinted from Takekawa et al: Pathological and immunohistochemical findings of an autopsy case of adult moyamoya disease. Neuropathology 24:236–242, 2004, with permission from John Wiley and Sons.](image3)
Moyamoya disease

TABLE 1: Proteins implicated in the pathophysiology of MMD and resulting concentrations of their overexpression in MMD

<table>
<thead>
<tr>
<th>Protein</th>
<th>Mature Protein Weight (kDa)</th>
<th>Amino Acid Residues</th>
<th>Mean Overexpressed Concentration in MMD</th>
<th>Mean Control Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF</td>
<td>45.024</td>
<td>1214</td>
<td>51.1%†</td>
<td>13.8%‡</td>
</tr>
<tr>
<td>bFGF</td>
<td>18.025</td>
<td>1464</td>
<td>64.0 pg/ml††</td>
<td>6.5 pg/ml††</td>
</tr>
<tr>
<td>HGF</td>
<td>103.024</td>
<td>728β‡</td>
<td>820.3 pg/ml††</td>
<td>a) 408.2 pg/ml††; b) 443.2 pg/ml††</td>
</tr>
<tr>
<td>TGFβ1</td>
<td>25.017</td>
<td>1121</td>
<td>31.0 ng/ml†</td>
<td>11.0 ng/ml†</td>
</tr>
<tr>
<td>G-CSF</td>
<td>19.623</td>
<td>1741</td>
<td>35.7 pg/ml§</td>
<td>19.6 pg/ml§</td>
</tr>
</tbody>
</table>

* Superscripted numbers refer to citations in the References section.
† Percentage of meningeal cellularity.
‡ HGF is transcribed as a 728 amino acid peptide and cleaved to fewer residues in its active form.

The presence of microthrombi is not specific to MMD and therefore is unlikely to provide a complete explanation for its pathophysiology.3 It is also worth noting that although an infectious etiology has been postulated, there has been no significant confirmatory evidence to date.38

Specific proteins known to be expressed in abnormal quantities in MMD have been investigated in an attempt to better understand the molecular pathophysiology of the disease (Table 1).

Vascular Endothelial Growth Factor. Vascular endothelial growth factor is a 45-kD homodimeric, basic glycoprotein that binds heparin to function.29 It plays a central role in pathological vasculogenesis and vascular permeability in intracranial lesions. Similarly, upregulated expression of VEGF-A165 in the β cells of pancreatic islets of Langerhans cells in mice has been shown to accelerate the onset of angiogenesis and tumor progression.8 Additionally, VEGF has been shown to promote angiogenesis in the setting of cerebral ischemia.27

In the setting of MMD, supraphysiological expression of VEGF is seen around the affected vasculature. In a study of 11 patients, Sakamoto et al.27 noted that the mean VEGF expression, or “meningeal cellularity,” was 51.1% ± 4.9% in MMD compared with 13.8% ± 5.9% in control patients. Whereas Takekawa et al.34 had previously identified VEGF in glial cells in autopsy studies of an adult MMD patient, Sakamoto et al. additionally localized VEGF to the dura mater in such cases. The presence of VEGF in the dura is an interesting finding that hints at extension of the pathological mechanisms of MMD beyond the cerebral vasculature. Although its excess concentration in MMD has been demonstrated, the specific role of VEGF in the pathophysiological mechanism of MMD remains unclear.

Basic Fibroblast Growth Factor. Basic fibroblast growth factor is an 18-kD protein generally made up of 146 amino acids.28 It normally stimulates the proliferation of mesodermal and neuroectodermal cells,26 and it has also been shown to induce growth of vascular smooth muscle and, when combined with VEGF, can play a leading role in angiogenesis.

Basic fibroblast growth factor has been shown to be abnormally elevated in the CSF of MMD.33,42 Takahashi et al.33 measured bFGF in the CSF of 15 patients with MMD (101 pg/ml) relative to patients with atherosclerotic and disc disease (8 pg/ml and 0 pg/ml, respectively). Yoshimoto et al.32 similarly demonstrated elevated bFGF concentration in the CSF of MMD patients compared with the control group; with the mean bFGF in the CSF of MMD patient of 64.0 pg/ml compared with 6.5 pg/ml in controls. Furthermore, the presence of bFGF has been noted in the abnormally thickened tunica media, leading Yoshimoto et al. to indicate that the high levels of bFGF in MMD contribute significantly to both the stenosis and angiogenesis.

Hepatocyte Growth Factor. Hepatocyte growth factor is one of the largest disulfide-linked cytokines, and in humans the protein is synthesized as a single-stranded 728 amino acid protein. The 95-kD peptide consists of a 60-kD heavy chain and 35-kD light chain. Proteolytic activation of HGF involves the release of a 31 amino acid N-terminal signal peptide. The active protein has been found to stimulate proliferation of rat hepatocytes and stimulate the growth of various epithelial, endothelial, and mesenchymal cells.28

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Transforming Growth Factor–β. Transforming growth factor–β is transcribed as a 390 amino acid peptide that is proteolytically activated to form the active 112 amino acid monomeric form of the active TGFβ, homodimer. It is a cytokine that is implicated in various cellular processes including cell growth, proliferation, and differentiation.4 In normal concentrations, TGFβ is involved in the expression cascade of various connective-tissue genes, whereas in supraphysiological concentrations it may contribute to pathological angiogenesis.12

Transforming growth factor–β has also been implicated in the pathogenesis of MMD. Upregulation of TGFβ has been demonstrated by Hojo et al.12 who re-
ported serum TGFβ1 levels in MMD patients of 31 ng/ml compared with 11 ng/ml in the control group. Furthermore, no significant difference in serum levels of TGFβ1 has been shown between patients with atherosclerosis and normal controls. Therefore, a specific correlation has been speculated between TGFβ1 and neovascularization in MMD. Additionally, TGFβ1 has been linked to the excessive production of elastin synthease, which is involved in intimal cell proliferation, a hallmark of MMD.

Granulocyte Colony-Stimulating Factor. Granulocyte colony-stimulating factor predominates as a 174 amino acid mature protein weighing 19.6 kD. It is a glycoprotein, growth factor, and cytokine, the main function of which is the stimulation of proliferation, survival, and maturation of neutrophil precursors and mature neutrophils.

An elevated concentration of G-CSF in the setting of MMD has been demonstrated by Ma et al. with mean serum G-CSF concentration of 35.7 pg/ml and 23.5 pg/ml in patients with MMD and controls, respectively. The role which G-CSF plays in the pathogenesis of MMD has yet to be elucidated.

Other Proteins. In addition to the aforementioned major proteins, other proteins have been found with limited evidence, to be elevated in MMD. Specifically, prostaglandin E2, interleukin-1β, and cellular retinoic acid binding protein 1β have been shown to be increased in concentration. Furthermore, Soriano and associates have demonstrated that several soluble endothelial adhesion molecules were elevated in the CSF of patients with MMD, suggesting chronic CNS inflammation. These included vascular cell adhesion molecule Type 1, intercellular adhesion molecule Type 1, and E-selectin. Additionally, hypoxia-inducible factor–1α, which promotes smooth-muscle cell proliferation in the presence of bFGF and HGF, is present in elevated levels in MMD.

Recently, Fujimura et al. examined the serum levels of MMP-2 and -9 in 16 patients with MMD. Both MMP-2 and -9 (gelatinase A and B, respectively) diminish the impenetrability of the blood-brain barrier by interrupting the endothelial basal lamina. Both MMP-2 and -9 are involved in the pathophysiology of cerebral ischemia, formation, and rupture of cerebral aneurysms, as well as other CNS pathologies. Fujimura et al. found the serum level of MMP-9 to be significantly higher in patients with MMD than in healthy controls (p = 0.0372). No significant difference was seen in serum MMP-2 levels between the groups. This first study of MMPs in MMD may indicate a contribution to the pathological vascular instability, indicating further study is necessary before conclusions can be drawn.

Genetics

It has been suggested that in some Japanese families MMD may be transmitted through a polygenic or autosomal dominant mode with low penetrance. Although familial occurrence accounts for approximately 9% of MMD cases, the majority of cases are sporadic. Linkage analyses have shown associations with loci 3p24.2–p26, 6q25, 8q23–28, 12p12, and 17q25 (Table 2).

In a linkage study of 16 Japanese families with familial MMD, Ikeda et al. reported that chromosome 3 was associated with MMD. They found that the patients’ microsatellite polymorphism mapped to chromosome 3p24.2–p26 with an MLS of 1.5. Other genes mapping to the 3p chromosome are those responsible for Marfan syndrome and the von Hippel–Lindau disease gene responsible for hemangioblastoma, and the authors suggest that the proposed locus on chromosome 3p may encode a gene product that is principally important for the formation and maintenance of vascular wall homeostasis.

A similar approach was taken by Inoue et al. with the analysis of chromosome 6. The authors performed a linkage study to confirm their hypothesis that familial MMD is associated with human leukocyte antigens (HLAs). The HLA gene is located on chromosome 6, and a marker in chromosome 6q25 was shared by 16 of 19 Japanese families with MMD that were studied. Human leukocyte antigens tend to be associated with virus-related tumors, autoimmune, and infectious diseases. Such associations are found in Takayasu arteritis and systemic lupus erythematosus. However, pathophysiological links between familial MMD and these other disease processes require further study.

A 2004 study by Sakurai et al. screened 12 nuclear families with MMD and found significant evidence for linkage to chromosome 8q23 (MLS 3.6) and suggestive evidence for linkage to 12p12 (MLS 2.3). The gene encoding TIEG (TGFβ–inducible early growth response) is located in chromosome 8q22.3. Because TIEG plays an active role in TGFβ expression, it may be a candidate gene for MMD. Another candidate gene located on chromosome 8q linkage is ANGPT1, a secreted ligand for TIE2, which is a receptor-like tyrosine kinase necessary for the normal development of vascular structures during embryogenesis. Furthermore, the authors proposed that EBA9 and DD5, a progestin-induced protein, may regulate angiogenesis through VEGF expression.

The study of chromosome 17 in relation to MMD began with Yamauchi et al. in their microsatellite linkage analysis. The characteristic lesions associated with MMD are occasionally seen in neurofibromatosis Type 1. The causative gene for neurofibromatosis Type 1 has been localized to 17q11.2. The research team members extracted leukocyte DNA from members of 24 families with MMD, and they subjected the DNA to polymerase chain reaction for 22 microsatellite markers on chromo-

<table>
<thead>
<tr>
<th>Gene Loci</th>
<th>MLS</th>
<th>Suggested Candidate MMD Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>3p24.2–p26</td>
<td>1.5</td>
<td>genes encoding Marfan syndrome &amp; von Hippel–Lindau disease</td>
</tr>
<tr>
<td>6q25§</td>
<td>1.6</td>
<td>HLA</td>
</tr>
<tr>
<td>8q23§</td>
<td>3.6</td>
<td>TIEG, ANGPT1, TIE2, EBAG9, DD5</td>
</tr>
<tr>
<td>12p12*</td>
<td>2.3</td>
<td>none</td>
</tr>
<tr>
<td>17q25†</td>
<td>3.1, 4.6†</td>
<td>BAIAIP2</td>
</tr>
</tbody>
</table>

* Two-point MLS.
† Multipoint MLS.

TABLE 2: Genetic loci associated with familial MMD and subsequent candidate genes at surrounding loci.

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They used both 2-point and multipoint linkage analyses and localized a gene for familial MMD on chromosome 17q25 (2-point MLS 3.1; multipoint MLS = 4.6). Recently, Mineharu and coworkers further investigated the involvement of chromosome 17 in MMD. The authors found that penetrance was partly age dependent and involved genomic imprinting, making it difficult to distinguish family members yet to be affected on a pedigree analysis. Furthermore, the group continued the sequence analysis work of Nanba et al., who isolated a 9cM region on chromosome 17q25, identifying candidate genes for MMD. One of the candidate genes, BAIP2, interacts with brain-species angiogenesis inhibitor–1 to inhibit bFGF, thereby inducing angiogenesis. Of the candidate genes selected, no mutations were identified, and therefore further study is needed to link MMD to chromosome 17q25.

Similar familial linkage studies conducted in the US have produced no clear results for the pathogenesis of MMD. Further research of genes susceptible to familial MMD presentation will help lead to a more complete understanding of the etiology and pathophysiology of the disease.

Conclusions

The pathophysiology of MMD remains unclear although several angiogenic and cellular proliferative proteins have been associated with the disease and correlated with the histopathological appearance of the diseased vessels. Similarly, studies have shown a familial linkage with a low-penetrance autosomal dominant or polygenic mode of transmittance at loci on chromosomes 3, 6, 8, 12, and 17. While our understanding of the pathophysiology at the molecular and genetic levels continues to expand, it is hoped that this novel knowledge will help guide innovative approaches and treatment modalities for this disease, including targeted intracranial bypass and biologically adapted stents.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Bendok. Acquisition of data: Weinberg, Arnaout, Rahme, Aoun. Drafting the article: Weinberg, Arnaout, Rahme, Aoun, Batjer. Critically revising the article: Bendok, Arnaout, Rahme, Aoun, Batjer.

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