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MOYAMOYA DISEASE: UNDERSTANDING THE SILENT CEREBROVASCULAR THREAT

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ABSTRACT

Moyamoya disease (MMD) is a rare cerebrovascular disorder characterized by progressive stenosis of the internal carotid artery (ICA) and its branches, leading to ischemia and hemorrhagic events. Although its precise etiology remains unclear, genetic and environmental factors play a role in the disease's development. Recent advances in diagnostic imaging, including dynamic susceptibility-weighted contrast-enhanced MRI, have improved the early detection and monitoring of MMD. Surgical revascularization techniques, such as direct and indirect revascularization, remain the primary treatment, although their long-term efficacy in preventing hemorrhagic events is still under investigation. Research into the disease's genetic and epigenetic mechanisms, including non-coding RNAs and DNA methylation, holds promise for enhancing diagnostic accuracy and developing personalized treatment strategies. This review consolidates the current understanding of MMD's genetic and epigenetic underpinnings, diagnostic challenges, and the future directions for clinical management.

KEYWORDS: Moyamoya disease, Ischemia, Hemorrhage, RNF213 gene, Genetic factors, angiogenesis, Revascularization, Epigenetics, DNA methylation, Non-coding RNAs, cerebrovascular disorders, Vascular remodeling.

INTRODUCTION

Moyamoya disease (MMD) is a uncommon condition with differing prevalence across various regions. It is marked by the gradual and ongoing narrowing of the distal (ICA) and its branches, including the anterior cerebral artery (ACA) and the middle cerebral artery (MCA). The disease is named after the hazy, smoke-like appearance of blood vessels at the base of the skull, as observed through digital subtraction angiography.[1]

Epidemiology

MMD is most commonly observed in East Asia, with a higher prevalence among women than men. Epidemiological research indicates an incidence rate of 0.94/100,000 people in Japan and 2.3/100,000 in South Korea. While most cases are sporadic, about 10 to 15% of individuals with MMD have a family history of the condition. Although the exact cause remains unclear, research suggests a potential link to chromosome 17. In regions outside East Asia, such as North America, the incidence rate is lower, around 0.09 per 100,000 people, but there has been a recent upward trend in cases.[1][2]

Etiology

Although significant progress has been made, the exact timeline of MMD progression and the precise pathophysiological causes are still not completely understood. However, evidence prefer that various factors, including angiogenesis, the immune system, genetics, and inflammation, might play a role in its development. Development of MMD has been linked to several factors related to angiogenesis, such as cytokines like endothelial colony-forming cells and vascular endothelial growth factor, basic fibroblast growth factor, transforming growth factor beta 1, and hepatocyte growth factor. Additionally, CD34-positive cells, mitochondrial abnormalities, and elastin mRNA and proteins expression are believed to contribute to MMD's onset and progression. Familial cases and strong association with specific ethnic groups suggest a genetic component in the disease.[3][4]

Clinical presentation

MMD can occur at any age, from childhood to adolescence. Most frequent symptoms are cerebral ischemia and intracranial hemorrhage. Early signs of the disease may involve ischemic strokes, hemorrhages, transient ischemic attacks (TIAs), cognitive difficulties, headaches, seizures, and movement disorders.[3] The most common presentations of Moyamoya disease are ischemic and hemorrhagic events, however, the frequency of these events varies between adult and pediatric patients. In children and adolescents, ischemia is

the predominant presentation, occurring in 73.9 to 97.5% of cases, while hemorrhage is very rare, occurring in just 2.5-8.0% of cases.[5][6] In first year after the initial presentation, there is an 18% chance of a symptomatic MMD recurrence, and the risk rises by 5% every year after that. Over 5 years, the cumulative risk is about 40%. Patients with lacunar infarcts also tend to experience better functional outcomes following revascularization.[7] A higher likelihood of future, severe hemorrhages is indicated by the presence of multiple microbleeds, which can also occur in the posterior communicating arteries.[8]

Diagnosis

Previously, diagnosing Moyamoya disease required bilateral steno-occlusive changes in the (ICA) for a definitive diagnosis. However, patients with unilateral terminal ICA steno-occlusion can now be included due to recent updates to the diagnostic criteria. Catheter angiography is needed for a definitive diagnosis in unilateral cases, although magnetic resonance angiography (MRA) or catheter angiography can be used to diagnose bilateral cases. Although catheter angiography remains the key diagnostic tool, it is invasive and associated with potential complications, so preprocedural precautions, such as adequate hydration, are essential, particularly for pediatric patients. Suzuki and Takaku's classification system outlines six stages of angiographic progression, but the stepwise progression from 1 to 6 stage has only been observed in a few cases, limiting its practical utility. Noninvasive tests like MRA and computed tomography angiography can identify steno-occlusion in the distal ICA or middle cerebral artery (MCA), but they are less effective at detecting basal collaterals. Modern diagnostic techniques are valuable for accurately diagnosing MMD, especially in the early stages according to Suzuki’s grading system.[9][10] The diagnosis, ongoing monitoring, and postoperative assessment of Moyamoya disease have all been enhanced by developments in imaging technology. Dynamic susceptibility-weighted contrast-enhanced MRI is one example; it is an effective and safe method to visualize how a gadolinium-based contrast agent flows. This allows for measuring cerebrovascular reserve capacity and brain perfusion in MMD patients.[11] Additional advanced MRI techniques, such as high-resolution vessel wall imaging and high-resolution MRI, offer the potential for early detection of vascular changes and assist in differentiating many causes of arterial stenosis. High-resolution MRI can identify the lack of a hyperintense juxta luminal band on T2-weighted images, along with narrowing of the middle cerebral artery and mild, uniform concentric wall enhancement in the distal ICA in individuals with Moyamoya disease. This contrasts with the eccentric wall thickening typical of atherosclerotic plaques.[12]

Mechanism of moyamoya disease

In contrast, atherosclerotic plaques are known to have eccentric wall thickening.[12]

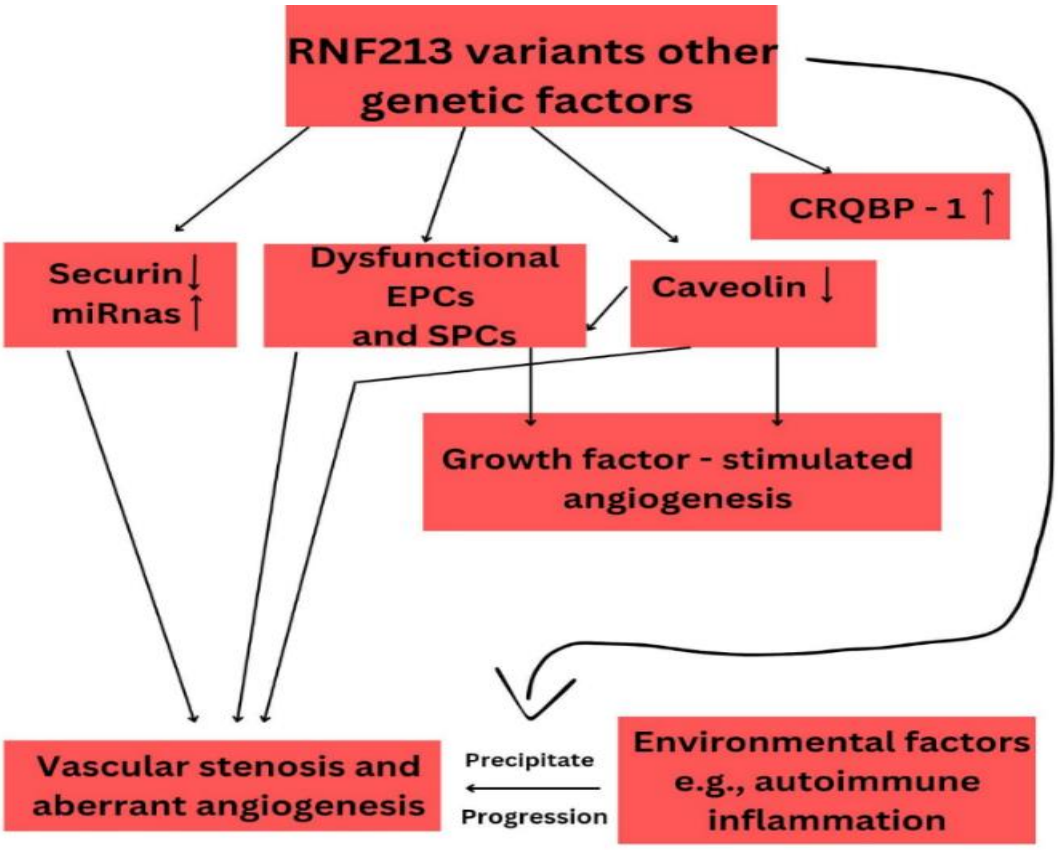

Figure 1: Mechanism of moyamoya disease.

Causes of moyamoya disease

1. ***Genetic factors***

RNF213 Gene: Mutations in the RNF213 gene, particularly the p.R4810K variant, are the primary genetic risk factors for Moyamoya disease (MMD). This gene is critical for vascular remodeling and the formation of new blood vessels, and the variant is notably prevalent among East Asian populations.

ACTA2 Gene: Changes in the ACTA2 gene, which is responsible for smooth muscle actin production, have been linked to certain cases of MMD, especially in familial settings.

Additional genetic loci: Other genetic regions have also been associated with MMD, suggesting that the disease has a multifaceted genetic basis.[13][14]

2. ***Genetic disorders***

Neurofibromatosis Type 1: Individuals with this genetic disorder have an elevated risk of developing MMD.

Down syndrome: There is an increased prevalence of MMD among people with Down syndrome.[15][16]

3. *Environmental factors*

Autoimmune disorders: Some studies suggest that autoimmune diseases may play a role in the development of MMD.

Infections: Certain infections may trigger or exacerbate the disease, though the exact pathways are not fully understood.[17][18]

The genetic basis of moyamoya disease

The vascular abnormalities, termed Moyamoya arteriopathy or vasculopathy, are classified into primary and secondary forms. The disease's early onset, familial tendencies, and variation in incidence among ethnic groups highlight a genetic basis. Research has identified several genetic loci and candidate genes, with limited replication of findings. The 17q25 locus has been implicated, and SNP studies have explored associations with vascular and inflammatory pathways.

The *RNF213* gene, strongly linked to MMD in East Asians, is the most significant genetic discovery. Although the exact role of *RNF213*, which encodes a large cytosolic protein, remains unknown, it is a confirmed susceptibility gene with a dosage-dependent effect on clinical outcomes. This opens avenues for genetic screening and potential therapeutic innovations. This summary emphasizes the genetic factors underlying primary MMD.[19]

Moyamoya syndrome

Moyamoya syndrome (MMS) is a rare disorder characterized by moyamoya angiopathy, which involves the gradual narrowing of cerebral blood vessels, primarily affecting the anterior circulation and, in some cases, the posterior circulation. MMS can be caused by acquired and inherited factors and is linked to various chromosomal and Mendelian diseases. The clinical expression and inheritance of MMS vary significantly, with some genetic conditions showing low penetrance (such as *NF1*, with 2.5%–6%) and others, like *BRCC3-MTCP1* deletions, exhibiting almost complete penetrance. MMS appears more frequently in Western countries compared to East Asia, partly due to the higher prevalence of sickle cell disease among populations of African ancestry.

Notable Genetic Causes of MMS

1. **ACTA2-Related Syndrome:** Mutations in the *ACTA2* gene, responsible for encoding smooth muscle alpha-actin, lead to a condition similar to moyamoya angiopathy. However, it is marked by arterial narrowing and abnormal circulation without the characteristic collateral vessels found in classic moyamoya.
2. **X-Linked MMS from *BRCC3*/*MTCP1* Deletions:** Caused by a deletion on the *Xq28* chromosome, this syndrome results in bilateral moyamoya angiopathy and is accompanied by symptoms such as short stature, heart issues, developmental delays, and hypergonadotropic hypogonadism. The loss of *BRCC3* and *MTCP1* impairs angiogenesis and DNA repair mechanisms.
3. **Moyamoya with Achalasia Due to *GUCY1A3* Mutations:** This condition, observed in consanguineous families, is caused by mutations in the *GUCY1A3* gene. It results in moyamoya, severe achalasia, and arterial hypertension. The mutations disrupt nitric oxide signaling, affecting smooth muscle function in both vascular and digestive systems.[20]

Table 1: Primary acquired and inherited causes of Moyamoya syndrome (MMS) and the essential diagnostic investigations when identifying moyamoya angiopathy.

Category	Possible Causes	Diagnostic Approaches
Acquired MMS	Exposure to radiation in the head or neck area	Patient interview
	Tumors at the skull base	Imaging studies of the skull base
	Arterial atherosclerosis in the skull base	Comprehensive imaging of the cervical arteries
	Chronic meningitis (e.g., tuberculosis) or cerebral vasculitis	Analysis of cerebrospinal fluid
	Inflammatory angiitis caused by autoimmune conditions	Blood tests for autoimmune markers (e.g., anti-nuclear antibodies)
	Blood clotting disorders	Tests for antithrombin, protein C and S levels, resistance to activated protein C and mutations in factor V Leiden or prothrombin
Inherited MMS	Sickle cell disease or carrier state	Hemoglobin electrophoresis, especially for individuals of African or Caribbean descent

Treatment

Currently, there is no conclusive evidence to support that drug treatments can stop or reverse the progression of moyamoya disease (MMD). Medications are mainly used to manage symptoms such as ischemia and hemorrhage by exerting anticoagulant or hemostatic effects.

The 2012 Japanese guidelines recommend antiplatelet drugs for ischemic MMD treatment, but there is still a risk of bleeding.

Surgical revascularization has proven effective in reducing ischemic stroke risk in ischemic MMD. However, its effectiveness in preventing recurrent bleeding in hemorrhagic MMD remains unclear. Research, including a review by Duan et al., indicates that surgical revascularization significantly lowers the recurrence rate of ischemia or hemorrhage compared to conservative treatments. A 2010 study in Japan found that surgery for hemorrhagic MMD effectively reduced rebleeding, with Kaplan-Meier analysis showing that the collateral circulation induced by surgery helped prevent further bleeding. These findings advocate for surgery in both ischemic and hemorrhagic MMD cases.

Three primary surgical revascularization techniques for MMD

Direct, indirect, and combined revascularization. Direct revascularization, such as superficial temporal artery-MCA anastomosis, is commonly used, with other anastomoses (like superficial temporal artery-ACA) for ischemic areas affected by hypoperfusion. Indirect revascularization methods utilize various tissues, such as encephalomyosynangiosis or encephaloduroarteriosynangiosis, to supply blood. Combined revascularization combines both direct and indirect methods. A recent meta-analysis suggests that direct or combined revascularization is more beneficial for adults with symptomatic or unstable MMD.

During the peri-operative period, it is particularly important to prevent ischemic complications, especially in pediatric patients. Direct vascular bypass surgery can lead to transient neurological dysfunction due to hemodynamic shifts, where blood flow from the superficial temporal artery competes with existing collateral circulation, disturbing cerebrovascular auto-regulation. Studies indicate that around 25% of patients undergoing direct bypass experience high perfusion symptoms, with increased risks in adults and hemorrhagic MMD patients. According to a PET scan study, these hemodynamic changes lead to high perfusion, which raises cerebral blood flow and volume while lowering the oxygen extraction fraction. Increases cerebral blood volume or oxygen extraction fraction before surgery increases the risk of high perfusion after surgery. Therefore, careful monitoring of blood pressure during the peri-operative phase is crucial to avoid complications related to excessive or inadequate perfusion.[21]

Advancements in Research and Prospective directions

Recent progress in comprehending disease mechanisms

Recent progress in Moyamoya disease (MMD) research has considerably enhanced our understanding of this complex disorder. A key development was the publication of revised diagnostic criteria for MMD in 2021 by Fujimura et al., which provides a scientific foundation for these updated guidelines and aims to share this critical information globally. Additionally, the 2021 Japanese Guidelines for Managing Moyamoya Disease, also developed by Fujimura et al., offer vital recommendations on the optimal approaches for treating the condition. The Japan Stroke Society and Research Committee on Moyamoya Disease provided feedback for creation of these guidelines.

Another significant advancement is the introduction of a novel hyperspectral imaging system by Iwaki et al., which holds promise in predicting postoperative cerebral hyperperfusion syndrome in MMD patients. This system analyzes cortical tissue and could transform how postoperative complications are identified and managed. Additionally, Kang et al. made a breakthrough by isolating smooth-muscle progenitor cells from MMD patients, creating a new experimental cell model for deeper research into the disease. This innovative approach enables an additional understanding of the disease's pathophysiology at cellular level. Lastly, Arias et al. conducted a thorough review of MMD, covering its clinical features, underlying mechanisms, surgical treatments, and patient outcomes.[22-25]

Recent studies on the epigenetic mechanisms involved in Moyamoya disease (MMD) have shed light on the role of various markers in the disease's development. Epigenetic mechanisms involve histone modifications, DNA methylation, and RNA-mediated processes, which are crucial for regulating gene expression. Abnormal regulation of these mechanisms in endothelial cells (ECs) and smooth muscle cells (SMCs) may contribute to vascular stenosis and the formation of moyamoya vessels, suggesting that epigenetic markers could be key to understanding MMD and identifying new biomarkers.

Surgical revascularization remains the important treatment for MMD, focusing on restoring blood flow and preventing strokes. However, challenges like poor postoperative collateral formation (PCF) and complications such as cerebral hyperperfusion syndrome persist. A deeper understanding of epigenetic mechanisms could improve preoperative assessments, leading to more precise surgical decisions.

Two studies have previously explored the methylome of MMD using DNA methylation arrays, but their scope was limited. Future research should aim to map the complete methylome of MMD and investigate the role of TET enzymes, which may offer protective effects against ischemic stroke. This could lead to new therapeutic targets for the disease.

DNA methylation in cell-free DNA (cfDNA) presents a promising non-invasive diagnostic approach, offering diagnostic information similar to its use in detecting fetal abnormalities, cancer, and transplant rejection. However, further research is needed to explore the potential of cfDNA methylation as a diagnostic tool for MMD.

The role of histone modifications in MMD remains under investigation, but recent advancements in HDAC-based diagnostics and treatments for cancer suggest that targeting histone modifications could provide novel therapeutic options for MMD.

Non-coding RNAs (ncRNAs), particularly miRNAs like miR-126, play a role in cerebrovascular diseases, including MMD. MiR-126 may aid revascularization and serve as a biomarker to predict PCF, guiding surgical decisions and improving treatment outcomes. Understanding ncRNAs in MMD could help personalize care and enhance patient outcomes.

Despite progress, challenges remain in translating epigenetic research into clinical practice, such as genetic variability, ncRNA degradation, and the influence of environmental and internal factors. Additionally, our understanding of the signaling pathways in MMD is still incomplete. Future studies using intracranial artery samples, in addition to peripheral blood or cerebrospinal fluid, may provide a more accurate understanding of the disease's molecular mechanisms.

Overall, while significant advances have been made in studying MMD's epigenetics, more research is required to clarify the role of epigenetic markers and their potential applications as diagnostic, prognostic, and therapeutic tools.[26]

CONCLUSION

Moyamoya disease (MMD) remains a complex disorder with unclear pathophysiology, though significant progress has been made in understanding its genetic, environmental, and epigenetic mechanisms. Improvements in diagnostic techniques, surgical revascularization, and research into epigenetic markers offer promising directions for improved diagnosis, treatment, and patient outcomes. Further research into histone modifications, DNA

methylation, and non-coding RNAs could conclude to more precise, personalized approaches to MMD management.

This article reviews the latest research on MMD, focusing on its genetic and epigenetic mechanisms, and discusses potential diagnostic and therapeutic innovations.

ABBREVIATIONS

MMD - Moyamoya Disease, ICA - Internal Carotid Artery, CA - Anterior Cerebral Artery, CA - Middle Cerebral Artery, TIA - Transient Ischemic Attack, RI - Magnetic Resonance Imaging - Magnetic Resonance Angiography, CT - Computed Tomography, PET - Positron Emission Tomography, NF1 - Neurofibromatosis Type 1, SNP - Single Nucleotide Polymorphism - Endothelial Cell, SMC - Smooth Muscle Cell, PCF - Postoperative Collateral Formation, cfDNA - Cell-Free DNA, ncRNAs - Non-Coding RNAs, miRNA – MicroRNA.

Declarations

Ethics Approval and Consent to participate

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Consent for publication

Not applicable.

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Authors' contributions

Dr. R. Redlin Jani: Critically reviewing and the manuscript for intellectual content, clarity, and accuracy.

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Composing: Draft Preparation: Creating the draft of the manuscript.

Writing: Analyzing and modifying what is written to make sure that it is precise, apparent and has intellectual content.

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Data availability

This manuscript does not report data generation or analysis.

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