Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Review Article

J Exp Clin Med
2024; 41(1): 201-209
doi: 10.52142/omujecm.41.1.33

Cerebrovascular enigma: Moyamoya disease etiology, identification, and management

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Received: 25.08.2023 • **Accepted/Published Online:** 25.02.2024 • **Final Version:** 29.03.2024

Abstract

Moyamoya disease is a sporadic cerebrovascular malady categorized by progressive stenosis of the internal carotid arteries and successive development of friable collateral vessels in the brain. The primary root of Moyamoya disease remains undefined, with a genetic predisposition playing an essential role. Familial cases show autosomal dominant inheritance patterns, Chained to particular genetic mutations. Genetic factors cooperating with environmental factors add to disease development. The moyamoya disease mostly occurs in East Asian countries like Korea and Japan. It has global impact. Its occurrence percentage shows demographic variations, with a greater prevalence among females and diverse age-related occurrence in childhood and adulthood. These patterns show genetic and environmental factors' interconnected linkage. Clinical Manifestations show transient, ischemic strokes, ischemic attacks and intracranial hemorrhages. Clinical signs vary between children and adults, with the later more susceptible to strokes. Cognitive impairment and motor discrepancies also arise due to compromised cerebral perfusion. Diagnosis depends on clinical assessment, neuroimaging, and angiography. Imaging techniques like Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) scans identify cerebral ischemic or hemorrhagic events. Cerebral angiography confirms the diagnosis by revealing a characteristic collateral vessel formation resembling a "puff of smoke." Treatment management includes revascularization procedures, such as direct or indirect bypass surgeries, to improve cerebral blood flow. Medical therapies, including antiplatelet agents, aim to reduce thrombotic risks. Continuing follow-up is crucial to calculate treatment-efficacy and disease progression.

Keywords: moyamoya disease, etiology, epidemiology, clinical presentation, diagnosis, treatment

1. Introduction

A chronic cerebrovascular illness called Moyamoya disease (MMD) is characterized by the gradual occlusion of the terminal internal carotid artery (ICA) and the ensuing development of collateral arteries (ICA), (MCA), and (ACA). Suzuki and Takeuchi in 1957 first referred to it as an unusual vascular illness (1). The special set-up of collateral vessels at the base of the brain is referred to as "moyamoya"(2). It is resembled as smoke coming out from a cigarette. By observing these images of smoke Suzuki introduce staging system for moyamoya disease Table 1. Cerebral hemorrhage and ischemia are the two manifestations of moyamoya. Cerebral angiography is the only test that can definitively diagnose MMD and separate it from malignancies (3). Despite being widespread around the world, MMD is most common in China, Korea, and Japan (4).

The fundamental causes and processes of MMD are still poorly understood despite its widespread prevalence. The ICA and the circle of Willis narrow due to this condition, which causes cortical micro vascularization with increased micro-vessel density and diameter (5, 6). The nature of moyamoya vessels, newly formed perforator arteries, and channel remodeling are details that have not yet been clarified (7). Histopathological alterations include media weakness, fibrin deposition, and hyperplastic smooth muscle cells or endothelium. The problem of scarce specimens and animal models hampers the investigation of MMD's mechanisms. In order to achieve appropriate assessment, MMD animal models that are grouped by species are now being prioritized (8–11). MMD is further defined by the ICA's progressive blockage, the development of collateral arteries, and genetic ramifications (12). Despite improvements, a thorough representation of MMD in animal models is still difficult to find, underlining the necessity of ongoing research to reveal the complexities of MMD (13, 14).

2. Materials and Methods

In this study, a widespread search was conducted across prominent health databases including PubMed, Cochrane, Embase, MEDLINE, and the Web of Science. Using a combination of keywords such as 'moyamoya disease,' 'etiology,' 'environment,' 'genetics,' 'epidemiology,' 'clinical

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presentations,' 'diagnosis,' 'treatment,' 'MRI,' 'stroke,' 'MRA,' and 'neurological,' the search aimed to systematically gather information on neurological health among stroke patients, with a specific focus on moyamoya disease. The research pursued to examine current approaches and established standards within this domain. Additionally, the review extended to scrutinize references within the selected studies to identify potentially overlooked articles, thereby ensuring a comprehensive synthesis of relevant findings.

Table 1. The Suzuki staging system (15)

Suzuki Stage	Description
Stage 1	Initial stage categorized by contraction or obstruction of the distal internal carotid arteries (ICAs). No collateral vessels are observed
Stage 2	Progressive stenosis or obstruction of ICAs with the emergence of basal moyamoya collaterals. Collaterals are fine and appear as haze or mist
Stage 3	Further stenosis or occlusion of ICAs with the development of more extensive moyamoya collaterals. Collaterals become more prominent.
Stage 4	Advanced stenosis or occlusion of ICAs. Moyamoya collaterals become robust, forming a network with clearer "puff of smoke" appearance
Stage 5	Terminal stage characterized by the regression of moyamoya collaterals and further vessel narrowing.
Stage 6	Complete occlusion of ICAs with minimal or no moyamoya collaterals. This stage is often associated with severe neurological deficits.

3. Etiology

Though the specific cause of Moyamoya disease (MMD) is unknown, a number of factors are thought to play a role in its progression. As a complex condition, MMD is thought to be the result of both hereditary and environmental influences. Following are some of the main features that are postulated to contribute to the etiology of Moyamoya disease

3.1. Genetics

The emergence of MMD appears to be significantly influenced by genetic factors. With roughly 10-15% of cases having a family history of the disease, there is a significant familial component (16). Numerous incidences of familial MMD have been linked to RNF213 gene mutations, especially in East Asian populations. However, not all cases of MMD are associated with this gene, indicating that there may be other genetic components at play (17). The following table (table 2) summarizes the genetic factors in moyamoya disease.

Table 2. Genetic factors and MMD

Genetic Factors and MMD	
Role of Genetic Factors in MMD	Increased frequency in certain ethnicities and lineages suggests genetic involvement (18)
Genome-wide Connotation Study (GWAS)	RNF213 identified as a vulnerability gene highly related with family MMD (9)
RNF213 Genetic Variant	Low-frequency variant c.14576G>A (p.R4810K) rises MMD danger in Asian populations (19)
RNF213 p.R4810K Mutations	Distributed into homozygous and heterozygous mutations; Homozygous mutation associated to earlier onset, severe symptoms, worse prognosis (20, 21)
Ethnic Variations in RNF213 Mutations	p.R4810K mutations not spotted in European MMD patients; Rare RNF213 variants recognized in Europeans (19)
Recent Study Findings	Other RNF213 mutations (besides p.R4810K) significant in Caucasians with MMD (12)

3.2. Vascular Abnormalities

The development of MMD is heavily influenced by abnormalities in the blood vessels, notably in the arteries delivering blood to the brain (22). These veins gradually constrict and eventually close, which reduces the amount of blood and oxygen reaching the brain.

3.3. Hemodynamic Factors

MMD may be brought on by irregularities in the blood flow patterns within the brain's blood vessels. Vascular constriction that reduces blood flow can trigger compensatory mechanisms that encourage the growth of collateral arteries in an effort to keep an adequate blood supply (6).

3.4. Inflammatory and Immune Factors

Some scientists think that immunological reactions and inflammation may also contribute to the etiology of MMD. The thinning and blockage of these vessels may be caused by inflammatory changes in the blood vessel walls (23).

3.5. Environmental Factors

There is some evidence to suggest that some environmental variables, such as infections or exposure to certain toxins, may contribute to the progress of MMD, especially in genetically susceptible individuals, even though the precise environmental triggers are not fully established (7).

4. Histological findings in Moyamoya disease (MMD)

Histological analysis of the brain's blood vessels, notably the arteries, reveals significant alterations (23). These alterations include non-inflammatory intimal thickening, changes to the vessel walls' structure, and the emergence of collateral vessels. Here are some of the main MMD-related histology findings:

4.1. Intimal Thickening
The thickening of the intima, the blood vessel wall's deepest layer, is one of MMD's defining characteristics. This non-inflammatory thickening can cause the vessel lumen to constrict and occlude (24).

4.2. Smooth Muscle Cell Proliferation
Hyperplasia, or increased proliferation of smooth muscle cells, is frequently seen on the walls of the afflicted arteries. This may contribute to the arteries' constriction and thickening of their walls (25).

4.3. Fibrin Deposition
Blood clotting protein fibrin, which can build up in the walls of the harmed arteries. This may also contribute to the blood flow disturbance and artery narrowing (26).

4.4. Elastic Lamina Changes
The elastic lamina, which gives the blood vessel walls their flexibility, can exhibit structural alterations. The flexibility and efficiency of the boats may be impacted by these alterations (27).

4.5. Collateral Vessels (Moyamoya Vessels)
The body strives to make up for the diminished blood flow brought on by the constriction and obstruction of the major arteries by developing collateral channels. A network of microscopic blood arteries known as "moyamoya vessels" form at the base of the brain, appearing as a “puff of smoke” in image (28).

4.6. Inflammatory Cells
Even while MMD causes a non-inflammatory thickening of the vessel walls, certain studies have found inflammatory cells inside the walls of the afflicted vessels. However, it is still unclear how inflammation plays a role in MMD (6).

5. Epidemiology:
The epidemiology pattern of Moyamoya disease (MMD) is different, and its prevalence and geographic distribution might vary (29). The East Asian nations, particularly China, Korea, and Japan, have the highest rates of MMD. With China reporting the highest number of cases, these areas have shown a considerable impact from the disease. MMD's influence is not limited to East Asia, though; cases have been reported elsewhere, albeit less frequently (table 3). In comparison to the East Asian hotspots, the incidence of MMD is significantly lower in places like North America (30).

Table 3. Epidemiology of Moyamoya disease

Aspect	East Asia (e. g., Japan, South Korea, China)	Other Regions (e. g., North America)
Incidence	High	Low, uphill drift in the US (31)
Prevalence (per 100,000)	10.5 (Japan), 16.1 (South Korea), 3.92 (Nanjing, China)	0.09 (Other regions), 2,430 cases reported in China since 1976 (32)
Age of start	Bimodal distribution: Major peak in first decade, moderate peak in late 20 to 30s	Bimodal distribution as above (32, 33)
Sex Distribution	Generally higher in females, male-to-female ratio ranges from 1:1.8 to 1:2.2	Sex ratio is 1:1 in China (32)

This table reviews the regional differences in the incidence, prevalence, age of start, and sex distribution of Moyamoya disease. Please note that the prevalence rates are specified for specific regions (East Asia and Other Regions) based on the delivered information.

MMD can affect people of all ages, with peaks in incidence occurring in childhood and during the fourth decade of life (3). The bimodal age distribution highlights the complex character of the disease's genesis and progression. Furthermore, it is clear that there is a gender bias because MMD is more common in women (34).

There have been reports of familial cases of MMD, raising the possibility that certain people may be genetically predisposed to the condition. This familial clustering emphasizes how genetic factors and illness development interact. Even while research into the precise causes of the geographic and demographic variations in MMD prevalence is still underway, it is most likely that a mix of genetic vulnerability and environmental factors play a role in these patterns (35).

6. Clinical Presentations
Ischemic symptoms are widespread in MMD patients and typically occur more frequently in young patients (28, 29, 36). These signs and symptoms are caused by the brain receiving less oxygen and blood. Temporary episodes of focal neurological impairments, such as weakness, numbness, or trouble speaking, might be a symptom of transient ischemic attacks (TIAs) (Fig. 1) (37, 38). Ischemic strokes can cause neurological abnormalities that are more severe and long-lasting, such as paralysis, speech difficulties, and sensory issues (39). Chronic cerebral hypo perfusion can potentially cause cognitive impairment and developmental delays in children. MMD can lead to hemorrhagic consequences, especially in adults. These occurrences include subarachnoid hemorrhage (bleeding into the area around the brain) and intracerebral hemorrhage (bleeding into the brain tissue) (40, 41).

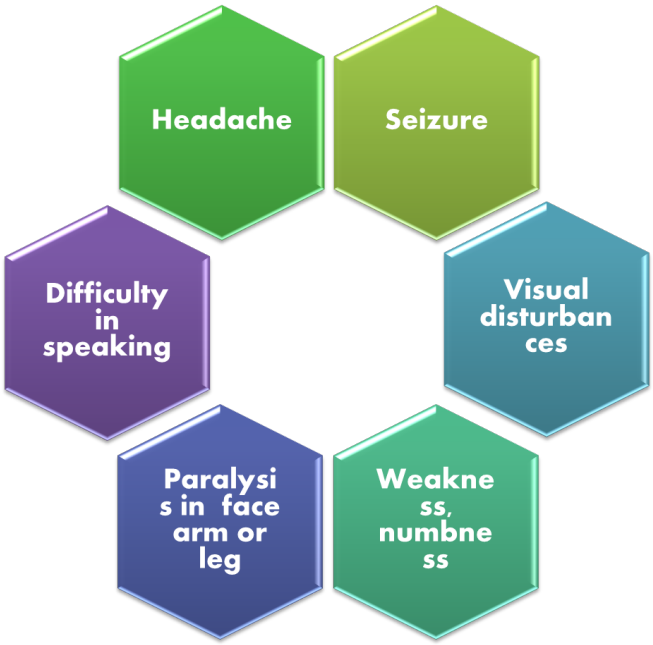

Fig. 1. Symptoms of the moyamoya disease

Hemorrhagic presentations can come on suddenly and severely, causing excruciating headaches, unconsciousness, neurological damage, and even coma. These occurrences may be brought on by the brittleness of aberrant blood vessels created as protective measures (42). Headaches that are both chronic and recurrent are a common symptom of MMD. These headaches could be chronic and severe, and they might be accompanied by other neurological symptoms. They are believed to develop as a result of changed blood flow patterns and added strain on the collateral arteries' dilated state (43–45). Particularly in cases involving young patients, seizures might be an unusual presentation of MMD. Sudden convulsions, altered consciousness, and uncontrollable movements are all symptoms of seizures. They may be brought on by abnormal brain electrical activity brought on by insufficient blood flow (46, 47).

7. Diagnosis

For the diagnosis of MMD, cerebral angiography continues to be the gold standard (3, 48–50). Invasive operation follows X-ray imaging, which injects a contrast dye into the blood arteries. The development of compensatory collateral vessels and bilateral distal internal carotid artery stenosis or blockage is the hallmark findings of MMD on cerebral angiography. On angiographic images, these collateral vessels, also known as "moyamoya vessels," produce a distinctive look resembling a "puff of smoke." In addition to helping with diagnosis, cerebral angiography offers important insights into the magnitude and severity of vascular abnormalities (table 4) (51–54). There is some other condition associated with moyamoya disease (fig. 2) (55, 56).

Table 4. Classification and scoring based on magnetic resonance angiographic (MRA) findings (57, 58)

Stage	Classification and Scoring based on MRA Findings
1	Mild - Narrowing of carotid fork
2	Moderate - Dilated major artery, slight moyamoya network
3	Moderate to Severe - Disappearance of anterior and middle cerebral arteries, distinctive moyamoya vessels
4	Severe - Posterior cerebral artery disappearance, lessening of singular moyamoya vessels
5	Very Severe - Main cerebral arteries vanish from internal carotid, reduced moyamoya, increased collateral pathways from external carotid
6	Extremely Severe - Moyamoya vessels disappear, cerebral blood flow from external carotid and vertebrobasilar systems

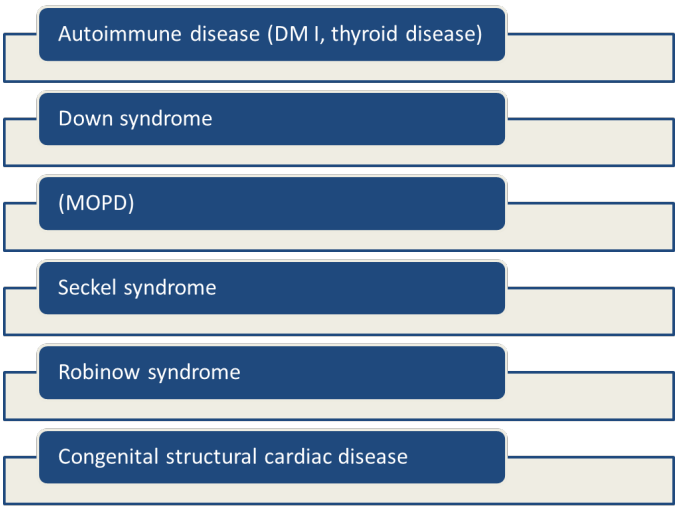

Fig. 2. Condition associated with moyamoya disease

The non-invasive imaging methods MRI and MRA provide comprehensive anatomical and vascular details without the requirement for contrast dye injection (7). A compromised blood flow can be seen on an MRI scan in the brain parenchyma as areas of ischemia or infarction. MRA, on the other hand, allows for the visualization of the blood vessels, making it possible to spot stenosis or occluded segments as well as the distinctive moyamoya collateral vessels (59, 60). These imaging techniques offer vital details regarding the course of the illness, the degree of vascular involvement, and potential sites of ischemia damage (61). There is an important guideline by observing the magnetic resonance angiographic findings (table 5). (57, 58).

Table 5. MRA findings

MRA findings	Score
Internal Carotid Artery	
Normal appearance	Score 0
Stenosis of C1 segment	Score 1
Discontinuity of C1 signal	Score 2
Complete absence (invisible)	Score 3
Middle Cerebral Artery	
Normal appearance	Score 0
Stenosis of M1 segment	Score 1
Discontinuity of M1 signal	Score 2
Complete absence (invisible)	Score 3
Anterior Cerebral Artery	
Normal A2 and its distal portion	Score 0
Decreased the signal in A2 and its distal portion	Score 1
Complete absence (invisible)	Score 2
Posterior Cerebral Artery:	
Normal P2 and its distal portion	Score 0
Decreased signal in P2 and its distal portion	Score 1
Complete absence (invisible)	Score 2

To indicate the severity of Moyamoya disease this cumulative mark is then used to define the MRA stage (table 6).

Table 6. MRA stages of Moyamoya Disease Severity

Stage	Score
MRA Stage 1	Total score of 0-1
MRA Stage 2	Total score of 2-4
MRA Stage 3	Total score of 5-7
MRA Stage 4	Total score of 8-10

The scoring and classification process based on magnetic resonance angiographic (MRA) results involves allocating scores to specific explanations related to blood vessels. These scores link to various aspects of the condition being evaluated. In table 5 the MRA findings are categorized into four key areas, and each observation is assigned a numerical score (62):

SPECT is a functional imaging method that measures cerebral blood flow. It follows the distribution of radiotracers inside the brain. In MMD, SPECT can identify areas of decreased blood perfusion, giving information about places where cerebral blood flow is impeded (63). This knowledge is helpful for determining how vascular alterations affect brain function and for making therapy options (64). Another way to assess cerebral blood flow and metabolism is by PET imaging. The regional cerebral blood flow, oxygen uptake, and glucose metabolism can all be quantified. Understanding how impaired blood flow in MMD impacts brain activity and metabolism can be helped by PET scans(65, 66).

Neuropsychological evaluations are essential for assessing cognitive function and locating probable abnormalities related to MMD. Memory, attention, language proficiency, and executive function are just a few of the cognitive functions that are assessed on these examinations (67). Neuropsychological testing can help determine the degree of cognitive impairment and direct actions to support patients' cognitive demands due to the potential influence of decreased blood flow on brain function (68). Genetic testing may be taken into consideration when there is a family history of MMD or when there are clinical characteristics that point to a genetic component (69). Especially in East Asian cultures, mutations in the RNF213 gene have been linked to familial occurrences of MMD. Making educated decisions about treatment can be aided by genetic testing, which can give useful insights into the underlying genetic factors causing the condition (11, 61).

8. Treatment

The main goals of medical care are to alleviate symptoms, avoid complications, and improve general health (70). Aspirin and other antiplatelet medications are frequently used to lower the risk of blood clot formation and lessen the likelihood of ischemic events (71, 72). Anticoagulant drugs may be used in some circumstances, but the possible benefits must be carefully balanced against the risk of bleeding (72). Controlling blood pressure is crucial to preventing weak blood vessels from rupturing, particularly in cases of hemorrhagic presentation. Regular follow-ups with neurologists and other specialists can help patients with MMD monitor their condition, change their medications, and handle any related medical conditions. Surgery is a crucial component of the therapy of MMD, especially for patients who are symptomatic or who are at high risk of serious consequences (73, 74). There are two main surgical options: direct revascularization procedures and indirect revascularization procedures.

Bypass surgery is used in direct revascularization methods to reestablish blood flow to the injured areas of the brain (75). The two main approaches are: Encephaloduroarteriosynangiosis (EDAS) is number one. Bypassing blocked portions, this method entails joining a healthy artery, often the superficial temporal artery to a cortical vessel. A direct source of blood flow to the damaged brain regions is what EDAS tries to give (76, 77). 2. Encephalomyosynangiosis (EMS) entails bridging the space between the bypassed vessel and the surface of the brain with a muscle flap. Over time, this method encourages the development of new blood vessels (78, 79).

Techniques for indirect revascularization are designed to speed up the body's normal mechanisms for gradually generating new blood vessels (80). The most popular technique is called pial synangiosis, in which the surgeon attaches healthy tissue or an artery to the surface of the brain. The transplanted tissue promotes the growth of new blood vessels over time, boosting blood flow to injured areas. The patient's age, the severity of the illness, the particular blood vessels affected, and other variables all affect the decision between direct and indirect revascularization. These surgical procedures are intended to improve overall neurological function, boost blood flow to the brain, and lower the risk of stroke. Supportive care and rehabilitation, in addition to medicinal and surgical treatments, are crucial components of MMD management (81–83). To track the disease's development and adjust

interventions as necessary, regular follow-up consultations with a multidisciplinary team that includes neurologists, neurosurgeons, and rehabilitation specialists are essential.

9. Conclusion

The Moyamoya disease stands as puzzling and complex cerebrovascular disorder that links genetic inclination with environmental influences. Regardless of its rarity, the influence of this disease echoes globally, with distinctive epidemiological arrangements give emphasis to its importance. The growing understanding of its composite etiology, determined by genetic mutations and other elements, discloses a deeper layer of cerebrovascular complexities. The clinical presentation of Moyamoya disease, manifest by ischemic and hemorrhagic events, emphasizes the urgent need for correct diagnosis and timely intervention. Improvements in neuroimaging and angiographic procedures have polished diagnostic precision, enabling clinicians to unravel the characteristic "puff of smoke" appearance that confirm the diagnosis. The emerging landscape of treatment profile comprises surgical revascularization and pharmaceutical interventions, show promise for enhancement of patient outcomes and checking further morbidity. As research continues to reveal the complicated nature of Moyamoya disease, the blend of genetic understandings, epidemiological information, and clinical skill is essential. Such integrative efforts show the way for enhanced tailored treatment strategies, deeper obligation of its global impact, and a broader understanding of cerebrovascular diseases as a whole. The pursuit to decode Moyamoya disease's mysteries remains an ongoing journey, highlighting the importance of collective research and innovation to solve its secrets for the betterment of affected individuals worldwide

Conflict of interest

No conflict of interest to declare.

Funding

The authors received no financial support for the authorship of this article.

Acknowledgments

None to declare.

Authors' contributions

Concept: M.A.A, S.A. A.K., Design: M.A.A, M.A, M.A., Data Collection or Processing: S.A, A.K., Analysis or Interpretation: M.A.A, M.A., And Literature Search: M.A.A., M.A., Writing: M.A.A., A.K.

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