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REVIEW

Infections in Moyamoya Phenomenon: Current Evidence and Future Horizons—Narrative Review

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Abstract: Moyamoya Disease (MMD) is a progressive cerebrovascular disorder characterized by the stenosis or occlusion of the terminal portions of the internal carotid arteries and fragile collateral vessel formation. While its etiology remains elusive, emerging evidence strongly implicates infections as key environmental triggers, particularly through immune-mediated vascular injury and interactions with genetic susceptibility (eg, RNF213 variants). This review explores the current understanding of the relationship between infections and MMD, examines epidemiological data, molecular and immunological mechanisms, genetic predispositions, and specific infections implicated in the disease. Critical limitations include causality ambiguity from reliance on anecdotal reports, methodological heterogeneity across studies, and mechanistic gaps in validating infection-endothelial dysfunction relationships. Future research must prioritize prospective cohorts and therapeutic strategies targeting infection-responsive pathways.

Keywords: moyamoya disease, RNF213, infection, second hit

Introduction

MMD is an uncommon and progressive cerebrovascular disorder. On angiographic imaging, the collateral vessel network exhibits an appearance resembling "a puff of smoke" which is derived from the Japanese term.[1] Epidemiologically, MMD exhibits an elevated incidence in East Asian populations (0.35–2.3/100,000 person-years), bimodal age peaks (5–10 and 30–40 years), and slight female predominance.[2–7] Clinically, MMD can lead to severe neurological complications, including recurrent ischemic strokes, transient ischemic attacks (TIAs), hemorrhagic strokes and cognitive impairments, thus posing significant challenges to the quality of life of affected individuals.[8,9] Although genetic factors such as mutations in the RNF213 gene and environmental influences are believed to play crucial roles in its pathogenesis, the exact etiology of MMD remains unclear. However, the low penetrance in genetically predisposed individuals suggests that a second hit may be required to trigger the onset of the disease.[10] The term Moyamoya syndrome (MMS) is often used when these vascular changes, also known as MMA, are observed in association with other conditions such as autoimmune diseases, meningitis, brain tumors, Down syndrome (trisomy 21), or type 1 neurofibromatosis, or following cranial irradiation.[1] Collectively, the frequent association of MMD with infection-related conditions (eg, meningitis in MMS) and the established requirement for "second hits" strongly position infections as pivotal environmental triggers that accelerate vascular pathology.[11]

A landmark 1983 cohort study first suggested infections as potential MMD triggers, reporting that 87% of patients (87/100) had antecedent facial/head infections.[12] However, nearly four decades later, this field remains critically understudied—with scant progress in validating causal links or mechanistic pathways. This persistent knowledge gap

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underscores an alarming stagnation in MMD etiology research. Exploring the relationship between infections and MMD is crucial for unraveling the multifaceted etiology of this enigmatic cerebrovascular disorder. Understanding how infectious agents may act as environmental triggers or modulators in individuals with genetic predispositions can shed light on the underlying mechanisms that drive arterial stenosis and the formation of fragile collateral vessels characteristic of MMD. Investigating this relationship could reveal novel insights into the inflammatory and immunological processes involved, potentially identifying preventable factors that contribute to disease onset and progression. Furthermore, elucidating the role of infections in MMD may lead to the development of targeted therapeutic strategies, enhance early diagnostic approaches, and inform preventive measures to mitigate the risk of severe neurological complications such as ischemic and hemorrhagic strokes. Ultimately, this exploration not only advances our comprehension of MMD pathogenesis but also holds promise for improving clinical outcomes and quality of life for affected individuals.

The primary goals of this review are to comprehensively summarize the current evidence linking infections to MMD, critically evaluate the existing understanding of the mechanisms by which infectious agents may influence the pathogenesis of MMD, identify significant gaps and inconsistencies within the current literature, and propose future research directions to address these unresolved questions. By synthesizing epidemiological studies, clinical case reports, and molecular research, this review aims to elucidate the potential role of various pathogens in triggering or exacerbating MMD, particularly in genetically susceptible populations. Additionally, it seeks to highlight areas where further investigation is needed, such as the interplay between genetic factors and infectious triggers, the specific inflammatory and immunological pathways involved, and the impact of different types of infections on disease progression. Ultimately, this review intends to provide a comprehensive framework that not only enhances our understanding of the relationship between infections and MMD but also informs the development of targeted prevention and therapeutic strategies, thereby improving clinical outcomes for individuals affected by this debilitating cerebrovascular disorder.

Overview of Moyamoya Disease

MMD and moyamoya syndrome are both cerebrovascular disorders characterized by the progressive stenosis or occlusion of the terminal portions of the internal carotid arteries and the proximal segments of the anterior and middle cerebral arteries, leading to the formation of abnormal collateral vessels that resemble a "puff of smoke" on angiographic imaging. The primary distinction between the two lies in their etiology: MMD is an idiopathic, primary condition with no identifiable underlying cause, predominantly affecting individuals of East Asian descent and presenting in a bimodal age distribution (children and adults). In contrast, moyamoya syndrome refers to moyamoya-like vascular changes - Moyamoya Phenomenon that occur secondary to other identifiable conditions or systemic diseases, such as genetic disorders (eg, Down syndrome), autoimmune diseases (eg, systemic lupus erythematosus), infections, or as a consequence of prior cranial irradiation. Clinically, while both conditions manifest with similar neurological symptoms including ischemic strokes, transient ischemic attacks, and hemorrhagic events, moyamoya syndrome requires addressing the underlying associated condition alongside managing the cerebrovascular abnormalities. Accurate differentiation between MMD and moyamoya syndrome is crucial for tailoring appropriate treatment strategies, which may involve surgical revascularization to improve cerebral blood flow and medical management targeting both the vascular lesions and the associated systemic disease.[1]

MMD and moyamoya syndrome exhibit distinct patterns of incidence and prevalence across various populations and age groups. MMD is most prevalent in East Asian countries, particularly Japan, Korea, and China, where it is considered a leading cause of cerebrovascular occlusive disease. In Japan, the annual incidence is approximately 0.35 per 100,000 individuals, with a prevalence around 3 per 100,000, making it significantly more common compared to Western countries.[2,13] In contrast, moyamoya syndrome, which encompasses moyamoya-like vascular changes secondary to other conditions, shows a broader distribution but remains relatively rare globally. In Western populations, including North America and Europe, the incidence of MMD is less than 0.1 per 100,000 individuals, categorizing it as a rare disease outside East Asia.[14] The disease exhibits a bimodal age distribution, with peaks in children (typically between 5 and 10 years old) and adults (usually between 30 and 50 years old). Pediatric cases often present with ischemic

symptoms such as transient ischemic attacks (TIAs) and strokes, while adult cases are more likely to present with hemorrhagic strokes due to the rupture of fragile collateral vessels.

Genetic factors, such as mutations in the RNF213 gene, are believed to contribute significantly to the higher prevalence in East Asian populations, while environmental factors may also play a role. Moyamoya syndrome can occur in any ethnic group but is influenced by the prevalence of underlying conditions like autoimmune diseases, infections, or genetic disorders, which can vary widely across different demographics. Increased awareness and advancements in imaging techniques have led to more frequent diagnoses globally, potentially reflecting both true increases in incidence and improved detection rates. Understanding these epidemiological trends is essential for developing targeted screening programs, optimizing diagnostic strategies, and allocating healthcare resources effectively, especially in regions with higher prevalence rates.[1]

MMD is a progressive cerebrovascular disorder marked by the narrowing or occlusion of the terminal internal carotid arteries and the proximal segments of the anterior and middle cerebral arteries, leading to the formation of fragile collateral vessels that resemble a "puff of smoke" on angiographic imaging. Clinically, patients commonly present with ischemic symptoms such as transient ischemic attacks (TIAs), strokes, chronic headaches, and, in advanced stages, hemorrhagic events due to vessel rupture. What's more, recent studies have confirmed that psychiatric symptoms induced by prolonged cerebral ischemia are not incidental comorbidities of moyamoya disease, but rather core components of its pathological mechanism. This finding highlights the essential biological nature of psychiatric symptoms within the clinical spectrum of moyamoya disease, demanding urgent attention in its diagnosis and treatment.[15] Diagnosis primarily relies on imaging studies, with cerebral angiography being the gold standard for visualizing arterial stenosis and collateral networks, while non-invasive techniques like MRI, MRA, and CTA are also essential for identifying characteristic vascular changes. Additionally, transcranial Doppler ultrasound can assess cerebral blood flow velocities, and advanced modalities like PET and SPECT may evaluate cerebral perfusion and metabolism. Accurate diagnosis involves distinguishing MMD from moyamoya syndrome by excluding secondary causes such as genetic disorders, autoimmune diseases, or infections. Early and precise identification of moyamoya through these diagnostic criteria and imaging findings is crucial for implementing effective treatments, including surgical revascularization, to restore adequate cerebral blood flow and prevent further neurological deterioration.[8]

Role of Infections in Neurological Disorders

Infections play a significant role in influencing neurological health and can contribute to the development and exacerbation of cerebrovascular diseases through a variety of mechanisms,[16–18] This pathological process is significantly associated with the clinical features of. MMD. Direct Pathogenic Effects occur when pathogens such as bacteria, viruses, fungi, or parasites invade the central nervous system (CNS), causing conditions like meningitis, encephalitis, and vasculitis. These infections can lead to vasculitis, resulting in vessel wall damage, narrowing, or occlusion, which increases the risk of ischemic strokes,[19–22] This shares pathological homology with the characteristic progressive intracranial vascular stenosis of MMD. For instance, Herpes Simplex Virus (HSV) can cause vasculitis leading to cerebral artery stenosis,[23] while HIV infection is associated with an increased incidence of stroke due to opportunistic infections and HIV-associated vasculopathy,[24,25] This is highly consistent with the vascular wall abnormal remodeling mechanism observed in the pathology of MMD. Indirect Mechanisms involve systemic inflammatory responses triggered by infections that affect the cerebrovascular system. Chronic infections, such as Chronic Periodontitis or Hepatitis C, can lead to persistent inflammation and endothelial dysfunction, promoting atherosclerosis—a major risk factor for ischemic stroke.[26,27] Inflammatory Cytokines released during infections (eg, interleukins,[28] tumor necrosis factor-alpha[29]) can destabilize atherosclerotic plaques, increasing the likelihood of plaque rupture and subsequent thromboembolic events.

Immune-Mediated Responses also contribute to cerebrovascular pathology. Autoimmune reactions triggered by infections can result in the body mistakenly attacking its own vascular tissues. For example, Post-Infectious Cerebral Vasculitis can occur following infections like varicella-zoster virus, leading to inflammation and narrowing of cerebral arteries, thereby increasing stroke risk.[30]

Molecular Mimicry is another critical mechanism where pathogen antigens resemble host proteins, causing the immune system to target both the pathogen and the host's vascular tissues. This phenomenon is implicated in conditions

such as Recurrent Infections with pathogens like dengue virus, which have been associated with vasculitic processes affecting the brain's blood vessels.[31] In patients with MMD, this immune cross-reaction may accelerate vascular wall injury. Especially when combined with dengue fever infection, molecular mimicry between pathogen antigens and vascular smooth muscle cell antigens can induce vascular remodeling abnormalities similar to those in MMD.

Neuroinvasive Infections such as West Nile Virus[32] and Japanese Encephalitis Virus[33] can directly damage neural and vascular tissues, leading to acute cerebrovascular events. These infections often result in acute inflammation, neuronal death, and disruption of the blood-brain barrier, facilitating further vascular damage and increasing stroke susceptibility.

Chronic Infections and Neurodegeneration, Persistent infections like H. pylori have been linked to increased risk of stroke through mechanisms involving chronic inflammation, oxidative stress, and modulation of lipid profiles, which collectively contribute to cerebrovascular disease progression.[34]

Infection-induced neurological damage results from a multifaceted interaction between inflammation, immune responses, and the direct effects of pathogens on the nervous system. When pathogens invade the central nervous system, they trigger an inflammatory response that can disrupt the blood-brain barrier, allowing immune cells to infiltrate and sustain chronic neuroinflammation, which may lead to neurodegeneration.[35–38] The immune system's efforts to eliminate the infection can sometimes mistakenly target neural tissues through mechanisms like molecular mimicry, resulting in autoimmune damage. Additionally, pathogens can directly harm neural cells by infecting and destroying them, releasing neurotoxins, and disrupting neural networks, which impairs cognitive and motor functions. These combined processes contribute to various neurological disorders, underscoring the importance of developing therapies that effectively modulate inflammation, regulate immune responses, and eliminate pathogens to protect and preserve neural integrity.

Evidence Linking Infections to Moyamoya Phenomenon

Epidemiological studies investigating the association between specific infections and the incidence of Moyamoya Phenomenon have explored various infectious agents and their potential role in triggering or exacerbating the condition. Several studies conducted in East Asian populations, where Moyamoya Phenomenon is more prevalent, have suggested links between viral infections—such as those caused by the varicella-zoster virus,[39] Epstein-Barr virus[40] and Leptospira[41]—and an increased risk of developing Moyamoya Phenomenon. For instance, a study indicated that EBV DNA was detected in 15 out of 20 patients with Moyamoya Phenomenon, significantly higher than the 4 out of 9 patients in the control group, suggesting a strong association between EBV and Moyamoya Phenomenon.[40] Additionally, some research has examined bacterial infections, including tuberculosis and meningitis, finding correlations that suggest chronic or severe bacterial illnesses might disrupt cerebral vasculature, thereby elevating moyamoya risk. As early as 1997, research findings by Japanese scholars indicated that Propionibacterium acnes and immunological factors might play a role in the pathogenesis of Moyamoya Phenomenon.[42] More and more studies have found that meningitis seems to be closely related to the progression of Moyamoya Phenomenon.[43–45]. Several case reports and small case series have highlighted potential connections between infections and the onset or exacerbation of Moyamoya Phenomenon. For instance, clinicians have documented cases in which patients—often children—developed transient ischemic attacks or strokes shortly after experiencing viral infections (eg, varicella-zoster, Epstein-Barr virus) or bacterial infections (eg, tuberculosis).[43,45–48] In these reports, neuroimaging frequently revealed newly formed or rapidly progressing stenotic lesions in the cerebral arteries characteristic of moyamoya. Although individual case reports cannot establish causation, they raise the hypothesis that an infectious insult may trigger vascular inflammation or immune-mediated damage in susceptible individuals, potentially accelerating the development of moyamoya. These case-based observations also underscore the variability in clinical presentation; in some instances, recovery from infection coincided with partial stabilization of vascular changes, whereas in others, progressive cerebral vasculopathy led to recurrent ischemic events.

Comprehensive analyses—such as meta-analyses and systematic reviews—have attempted to synthesize the growing yet disparate body of research linking infections and moyamoya.[39,43,49,50] These reviews often combine epidemiological data, case series, and mechanistic studies to explore whether certain pathogens or infection types are consistently associated with moyamoya. Some reviews identify a modest but notable correlation with specific viruses (eg, herpesviruses) and chronic bacterial infections (eg, tuberculosis), suggesting that persistent immune activation or direct vascular

injury could contribute to disease pathogenesis. However, the overall findings remain inconclusive, largely due to small sample sizes, regional variability, and heterogeneity in study designs. Many reviews call for more robust, multicenter prospective studies with standardized diagnostic criteria for both moyamoya and infections of interest. This would help clarify whether infections act as a true causative factor, a catalyst in genetically predisposed individuals, or merely a coincidental event in the complex pathophysiology of Moyamoya Phenomenon.

In Summary, the evidence remains inconclusive—not merely due to disease rarity—but fundamentally because of irreparable methodological flaws across existing studies. Severe limitations compromise all current data: ecological analyses fail to control for genetic/environmental confounders; case reports (eg, EBV/VZV associations) lack temporal proof of infection preceding vascular pathology; and bacterial studies (eg, tuberculosis, meningitis) demonstrate inconsistent diagnostic criteria and selection bias. Critically, meta-analyses confirm that heterogeneity in study designs, outcome measures, and pathogen screening renders pooled estimates uninterpretable Consequently, no decisive conclusions can be drawn regarding clinical significance—whether infections initiate vasculopathy, accelerate progression, or merely represent epiphenomena. This field currently rests on weak and inconclusive evidence; purported associations require validation through multicentric prospective cohorts with prespecified causal inference methods (eg, Mendelian randomization) before mechanistic or clinical roles can be established.

Pathophysiological Mechanisms Connecting Infection and Moyamoya Phenomenon

Infections may incite inflammatory cascades that alter cerebral vessel integrity and function, potentially contributing to the characteristic vascular stenosis and abnormal collateral network of Moyamoya Phenomenon.[51] When a pathogen invades, immune cells (eg, macrophages, T cells) and resident vascular cells (eg, endothelial cells, smooth muscle cells) become activated and release pro-inflammatory cytokines[52] (like TNF-α, IL-1β, IL-6) as well as matrix metalloproteinases (MMPs), which degrade extracellular matrix components and can weaken vessel walls. This inflammatory milieu promotes endothelial dysfunction, smooth muscle cell proliferation, and intimal hyperplasia, all of which narrow the arterial lumen and reduce blood flow. Over time, chronic or recurrent inflammatory insults from persistent or repeated infections may sustain these pathologic processes, particularly in individuals with underlying genetic or immunological predispositions.[53] This interplay between infection-induced inflammation and vascular remodeling helps explain how infectious episodes could serve as a key trigger or accelerator in the development and progression of Moyamoya Phenomenon.

Immune-mediated processes, particularly autoimmunity and dysregulation of immune surveillance, are increasingly recognized as contributors to moyamoya pathogenesis. Certain genetic predispositions—such as specific HLA haplotypes—may make individuals more prone to mounting aberrant immune responses against components of the cerebral vasculature. In some cases, molecular mimicry following an infection can lead to autoantibody or autoreactive T-cell development that targets endothelial antigens, prompting chronic inflammation and remodeling of the vessel wall. This immune-driven injury can exacerbate endothelial dysfunction, intimal thickening, and smooth muscle cell proliferation, ultimately narrowing arterial lumens and disrupting cerebral blood flow.[54] Over time, these processes may culminate in the hallmark "moyamoya" vascular pattern, suggesting that inappropriate or sustained immune activity plays a pivotal role in both initiating and perpetuating the disease.

Certain pathogens have the capacity to directly infect or damage the endothelial and smooth muscle cells that line cerebral arteries, potentially initiating the vascular abnormalities seen in Moyamoya Phenomenon. For example, viruses like varicella-zoster or HIV can infect endothelial cells, causing cell death, inflammation, or dysfunction at the vessel wall.[55,56] Bacterial pathogens—especially those associated with meningitis or chronic infections—may release toxins or enzymes (eg, proteases) that degrade structural proteins, weaken vessel integrity, and stimulate local inflammatory responses. These direct, infection-mediated injuries can trigger reparative processes (eg, intimal hyperplasia) that lead to progressive narrowing of the arterial lumen. Over time, repeated cycles of infection, endothelial damage, and repair may culminate in the characteristic stenotic lesions and collateral formation characteristic of Moyamoya Phenomenon.[57]

Genetic susceptibility and environmental exposures, such as infections, likely intersect to influence the pathogenesis of Moyamoya Phenomenon. Individuals carrying certain genetic variants—particularly those affecting immune regulation or vascular homeostasis—may be more prone to abnormal inflammatory responses, endothelial dysfunction, and

arterial remodeling after encountering specific pathogens. In these genetically susceptible individuals, an infectious trigger can exacerbate or accelerate vascular injury, leading to the progressive narrowing and collateral vessel formation characteristic of moyamoya. This gene-environment interplay helps explain why many patients with moyamoya also exhibit family histories of stroke or autoimmune disorders, and why the disease clusters in certain populations. Ultimately, a combination of inherited risk factors and infectious insults—possibly through immune-mediated, inflammatory, or direct vascular injury mechanisms—can synergize to drive moyamoya pathogenesis.

However, constrained by the current limitations of MMD research, this review can only propose mechanistically plausible hypotheses regarding disease etiology; conclusive evidence establishing the precise pathophysiological mechanisms of moyamoya disease remains absent, necessitating further investigation with higher-grade evidence.

Genetic Factors and Susceptibility to Infection-Related Moyamoya Disease

MMD exhibits a significant genetic component, with several key genes identified that influence an individual's susceptibility to the condition. The most prominent among these is RNF213, a gene located on chromosome 17q25. RNF213 encodes a protein involved in angiogenesis and vascular development, playing a critical role in maintaining the structural integrity and function of cerebral arteries. A specific variant of RNF213, known as p.R4810K, is strongly associated with MMD, particularly in East Asian populations such as Japanese and Korean individuals, where this mutation is present in a substantial proportion of cases. This variant is believed to impair the normal angiogenic processes, leading to abnormal vascular remodeling and the progressive stenosis of the internal carotid arteries that characterizes moyamoya.[10,58–60]

Genetic predispositions interact with environmental factors, such as infections, to modulate MMD risk. Individuals carrying susceptible genetic variants like RNF213 may exhibit heightened inflammatory responses or impaired vascular repair mechanisms following infectious insults, thereby accelerating the pathological vascular changes seen in moyamoya. Furthermore, genetic studies have revealed population-specific differences in MMD prevalence and genetic associations, underscoring the interplay between genetic background and environmental exposures in disease manifestation.[58]

In recent years, research on the key gene RNF213 of MMD has gradually deepened. Bhardwaj et al have shown that MMD variants indeed lead to a decrease in E3 activity and ubiquitination, having a dominant negative effect on the oligomeric structure of RNF213. The authors believe that the reduction in RNF213 E3 ligase activity is at the core of the pathogenesis of MMD. They even hypothesize that the degree of damage may be related to the penetrance level of certain MMD polymorphisms.[61] Baseline expression of RNF213 has been observed in many tissues, but the expression is upregulated by LPS, TNFα, and IFN, indicating that infection signals are involved in the occurrence and development of MMD through RNF213.[62,63] Recent study by Elsje G Otten has shown that RNF213 has been identified as a novel immune sensor, uncovering an unexpected link between MMD and infections. Although the ability of the RNF213 allele susceptible to MMD to ubiquitinate LPS remains unimpaired, activation of mutant RNF213 by bacteria or other infections may still lead to the development of MMD in susceptible individuals.[64]

When genetically predisposed individuals encounter infections—whether viral (such as varicella-zoster virus or Epstein-Barr virus) or bacterial (like tuberculosis)—their immune and vascular systems may respond aberrantly due to the underlying genetic mutations. For instance, the RNF213 variant may impair normal endothelial cell function and angiogenesis, exacerbating the inflammatory response triggered by an infection.[65,66] This heightened inflammatory state can lead to increased production of pro-inflammatory cytokines (eg, TNF-α, IL-6) and matrix metalloproteinases (MMPs), which degrade the extracellular matrix and weaken vessel walls. Consequently, this environment fosters endothelial dysfunction, smooth muscle cell proliferation, and intimal hyperplasia—key pathological features of moyamoya.

Moreover, genetic factors may influence the degree of immune system dysregulation following an infection. Variants in genes involved in immune regulation (such as those affecting the TGF-β signaling pathway) can predispose individuals to more robust or chronic inflammatory responses. This sustained inflammation can perpetuate vascular damage and impede proper vascular repair mechanisms, accelerating the stenosis of cerebral arteries characteristic of MMD. Additionally, genetic predispositions might enhance the likelihood of autoimmune reactions through mechanisms like molecular mimicry, where the immune system erroneously targets vascular tissues following an infection.

In summary, gene-environment interactions in MMD involve the convergence of genetic susceptibility—primarily through mutations like those in RNF213—and environmental triggers such as infections (Figure 1). These interactions amplify inflammatory and immune-mediated responses, leading to vascular alterations that drive the development and progression of moyamoya. Understanding these complex relationships is essential for identifying at-risk individuals, developing preventive strategies, and tailoring therapeutic interventions that address both genetic vulnerabilities and environmental exposures.

However, the current conceptualization of RNF213 as an infection-susceptibility factor in moyamoya disease remains fundamentally speculative due to the absence of empirical validation across three critical domains. While the p.R4810K variant demonstrates epidemiological association with East Asian MMD, its proposed mechanistic functions—including pathogen sensing, interferon dysregulation, or molecular mimicry—derive solely from computational models and non-physiological in vitro systems rather than disease-relevant evidence. Persisting knowledge gaps include: the lack of experimental confirmation for direct RNF213-pathogen interactions in human cerebrovascular cells; the failure of existing animal models combining Rnf213 mutations with infection challenges to recapitulate human vasculopathy; and contradictory human tissue evidence showing negligible RNF213 expression in affected intracranial arteries. Consequently, the paradigm must be recognized as an unsubstantiated hypothesis. To resolve this stagnation, rigorous mechanistic validation is urgently needed: CRISPR-engineered iPSC-derived endothelial cells should interrogate infection-induced immune pathway activation; conditional Rnf213$^{-/-}$ murine models must assess vascular remodeling dynamics during timed CNS infections; and multiplex serological profiling of MMD cohorts should test for pathogen-specific antibody cross-reactivity. Without such targeted experimentation, the biological relationship between RNF213, infections, and moyamoya pathogenesis will remain scientifically unanchored.

Clinical Implications

Understanding the infection - moyamoya link can greatly improve diagnostic strategies. Clinicians are encouraged to take detailed patient infection histories, including past viral and bacterial exposures, and assess the infection - symptom onset timing. This leads to targeted infectious disease testing (eg, serological and molecular assays) and guides the use of advanced imaging (MRA or CTA) for vascular change identification.[67,68] Evaluating inflammatory markers and genetic testing for genes like RNF213 (especially in those with relevant family histories or ethnic backgrounds) are also key in diagnosis.[69] Integrating patient histories, targeted testing, and specialized imaging helps clinicians better distinguish moyamoya from other conditions, enabling earlier and personalized interventions for both infections and genetic

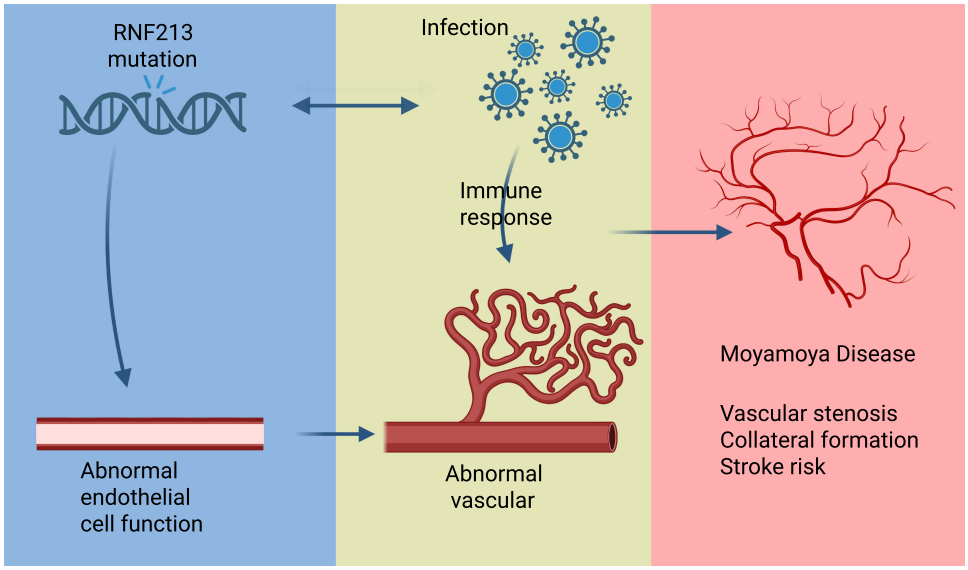

Figure 1 Mechanism Diagram of the Association Between Moyamoya Disease and Infection.
Notes: Created in BioRender. Zihan, W. (2025) https://BioRender.com/by6fh9u.

predispositions, thus improving patient outcomes. However, such integrated treatment approaches remain largely idealized and clinically impractical to implement; consequently, exploring effective, feasible therapeutic strategies remains an urgent priority.

Effective moyamoya treatment needs a comprehensive approach. It combines antimicrobial therapies to manage triggering or exacerbating infections, reducing inflammation and preventing more vascular damage.[70] Immunomodulatory treatments like corticosteroids, immunosuppressants, and IVIG control abnormal immune responses and chronic inflammation causing artery narrowing. Surgical interventions like STA - MCA bypass and EDAS restore brain blood flow and lower ischemic risks.[71–73] What' more, for psychiatric symptoms in MMD, antipsychotics (eg, risperidone, paliperidone) demonstrate efficacy in 83% of patients experiencing hallucinations/delusions. Surgical interventions such as encephaloduroarteriosynangiosis show selective effectiveness for symptoms definitively linked to hypoperfusion, yet only 31% of psychotic symptoms improve postoperatively. This evidence underscores that clinical practice must integrate cerebrovascular pathology with psychiatric phenotyping: psychiatric screening should target left-hemisphere lesions or posterior circulation involvement in psychotic presentations, while neurology services should perform MRA evaluations for first-episode treatment-refractory psychosis. Multidisciplinary collaboration is essential to balance pharmacotherapy, surgical options, and cognitive rehabilitation—siloed management of psychiatric symptoms without addressing the underlying vascular pathology must be avoided.[15] With personalized medicine and multidisciplinary cooperation, integrating these strategies addresses both vascular problems and infectious/immune factors, ensuring holistic management and better patient outcomes.

The history of infections in patients with MMD can significantly influence both the progression of the disease and the overall patient outcomes. Infections may act as triggers that accelerate the vascular pathology inherent to moyamoya, leading to more rapid disease progression and potentially more severe neurological deficits.[43,44,50,74,75] For instance, patients with a history of recurrent or chronic infections may experience sustained inflammatory and immune-mediated damage to cerebral arteries, exacerbating arterial stenosis and diminishing cerebral blood flow more quickly than in patients without such infection histories. This heightened inflammatory state can increase the frequency and severity of ischemic events, such as transient ischemic attacks (TIAs) and strokes, thereby worsening functional outcomes and quality of life. Additionally, infection-related complications can complicate surgical interventions, such as revascularization procedures, by increasing the risk of postoperative infections, delaying recovery, and potentially reducing the efficacy of surgical treatments. Patients with significant infection histories may also exhibit poorer responses to immunomodulatory therapies due to altered immune system dynamics, necessitating more tailored and aggressive treatment approaches. Epidemiological studies suggest that individuals with prior severe infections may have a higher likelihood of developing more extensive moyamoya vasculopathy, leading to increased dependency and long-term disability.[12] However, there are still relatively few studies in this area, and more research is needed to corroborate this conclusion. Nevertheless, it is certain that a history of infections is associated with a more challenging disease course, requiring comprehensive and multidisciplinary management strategies to optimize patient outcomes.

Current Research and Knowledge Gaps

Recent studies investigating the relationship between infections and MMD have provided suggestive evidence of an association, particularly in genetically predisposed populations such as those with RNF213 mutations common in East Asians. Epidemiological research indicates that viral infections like varicella-zoster virus,[39] Epstein-Barr virus,[40] and even SARS-CoV-2 may act as environmental triggers[76] that exacerbate vascular inflammation and remodeling characteristic of moyamoya. Case reports have highlighted instances where moyamoya-like vasculopathy follows acute or chronic infections, while current research acknowledge a modest association but note inconsistencies and the need for larger, more diverse studies.[77] Molecular and genetic investigations are beginning to elucidate mechanisms involving immune-mediated vascular damage and gene-environment interactions, although definitive causal pathways remain unclear. Additionally, emerging research explores the role of chronic bacterial infections and the potential impact of the microbiome on moyamoya pathogenesis.[42] Overall, while recent findings support a plausible link between infections and MMD, significant gaps remain, including inconsistent pathogen associations, limited mechanistic insights, and the need for standardized, longitudinal studies to establish causality and inform integrated treatment strategies.

Despite growing interest, significant gaps remain in understanding the infection - moyamoya link. Epidemiological data are limited and region - focused, making it hard to generalize results. The roles of specific pathogens are inconsistently identified, with conflicting study results. Mechanistic insights into infection - related moyamoya development are insufficient, especially regarding immune - mediated and vascular processes. The complex interactions between genetic predispositions and environmental factors are not well understood. There's a lack of standardized criteria and methods, complicating research comparison. Longitudinal and prospective studies are scarce, hampering causal relationship establishment. Emerging and rare pathogens are underexplored, and multi - omics applications are minimal. Also, clinical guidelines do not fully incorporate infection history. Closing these gaps needs comprehensive, standardized, multidisciplinary research to clarify pathogen roles, mechanisms, and develop integrated strategies.

The current evidence linking infections to moyamoya disease is fundamentally compromised by irreparable methodological weaknesses that collectively invalidate causal inferences and clinical applicability. Epidemiologically, overreliance on East Asian cohorts (eg, RNF213-mutant populations) introduces selection bias preventing generalizability, while retrospective designs universally fail to establish if infections temporally precede MMD onset—a critical flaw exemplified by SARS-CoV-2 case reports erroneously inferring causality from coincidental timing. Mechanistically, non-physiological in vitro models of immune-mediated vascular damage lack in vivo verification, rendering proposed pathways biologically implausible; similarly, claims of RNF213-pathogen interactions rely exclusively on computational predictions without functional validation in human cerebrovascular cells, reducing genetic-environmental hypotheses to oversimplified speculation. Crucially, lots of studies neglect confounding by regional endemic infections, socioeconomic factors, and comorbidities that independently modulate immune responses, compounded by publication bias favoring dramatic case reports that overrepresent viral associations (EBV/VZV) while omitting negative findings. Further noise stems from irreconcilable heterogeneity: variable MMD diagnostic criteria and pathogen detection methods preclude meta-analytic synthesis, and arbitrary pathogen selection overlooks prevalent bacterial/fungal triggers to generate artifactual "significant" associations. Consequently, the purported infection-MMD link remains a methodologically generated artifact rather than an evidence-based paradigm; absent prospective cohorts employing causal inference techniques (eg, Mendelian randomization), this field lacks scientific anchorage for clinical translation.

Future Directions

Future research on the infection - moyamoya link should prioritize longitudinal designs to clarify temporal and causal relationships. Larger, diverse - cohort studies across multiple regions can enhance generalizability and identify population - specific risks. Standardizing diagnostic criteria and methods for moyamoya and infections is crucial for consistency. Mechanistic experiments using in vitro and in vivo models are needed to uncover biological pathways. Integrating multi - omics approaches (eg, single-cell transcriptomics, spatial transcriptomics, spatial metabolomics, etc) can offer insights into gene - environment interactions and find biomarkers. Exploring emerging/rare pathogens and the microbiome's role will broaden understanding of environmental triggers. For example, for the psychiatric symptoms associated with moyamoya disease, functional magnetic resonance imaging (fMRI) can be used to dynamically monitor the brain functional connectivity of MMD patients. Combined with positron emission tomography (PET) to track the distribution of neurotransmitters (such as dopamine and serotonin), the brain metabolic differences between patients with left/right hemisphere lesions can be compared. A registration system for psychiatric symptoms in MMD patients should be established. Combined with genome-wide association studies (GWAS), risk genes (such as HLA complex and cytokine genes) can be screened, and Mendelian randomization can be used to exclude reverse causal bias. Biomarkers can be screened through multi-omics analysis of the blood and diseased blood vessels of such patients. These strategies will fill gaps, deepen mechanistic understanding, and help develop integrated diagnostic and therapeutic approaches for better patient outcomes.

Targeting infection - related pathways holds great potential for MMD treatment innovation. New approaches may include targeted antimicrobials to clear implicated pathogens, advanced immunomodulatory therapies like cytokine - inhibiting biologics, gene therapy for genetic predispositions, personalized medicine using multi - omics, and emerging therapies such as neuroprotective agents and stem cell therapies. Combining these with surgical revascularization could

offer a comprehensive treatment. Research and trials are needed to validate their safety and efficacy for more effective, personalized moyamoya management.

Implementing effective public health strategies for infection prevention could play a crucial role in reducing the incidence of MMD, particularly by targeting infections that may act as environmental triggers in genetically susceptible populations. Key strategies include widespread vaccination programs against common viral pathogens like varicella-zoster virus and Epstein-Barr virus, which have been associated with moyamoya development. Enhancing hygiene practices and infection control measures in communities, especially in regions with high moyamoya prevalence, can minimize the spread of these pathogens. Early detection and prompt treatment of acute and chronic infections through robust healthcare infrastructure and accessible medical services are essential to prevent prolonged inflammatory and immune-mediated vascular damage. Public health campaigns aimed at raising awareness about the potential link between infections and moyamoya can encourage timely medical consultation and adherence to preventive measures. Additionally, integrating genetic screening for known susceptibility genes such as RNF213 in high-risk populations could help identify individuals who might benefit from targeted infection prevention strategies. Collaborative efforts between healthcare providers, researchers, and policymakers are necessary to develop and implement comprehensive prevention programs that address both infectious and genetic risk factors, ultimately aiming to lower the burden of MMD through proactive public health interventions.

Discussion

Environmental triggers for MMD in genetically predisposed individuals, potentially through immune-mediated mechanisms such as systemic inflammation, molecular mimicry, or autoimmune responses targeting cerebral vasculature. While genetic factors like RNF213 mutations are central to MMD susceptibility, infections could serve as a "second hit" accelerating disease onset, especially in pediatric cases where post-infectious temporal associations are reported.[12] However, the current understanding of the association between infections and moyamoya phenomenon is constrained by several methodological limitations. A substantial proportion of existing evidence derives from isolated case reports and small case series, which are inherently susceptible to selection bias and publication bias. The predominance of retrospective studies and anecdotal observations introduces heterogeneity in diagnostic criteria, pathogen identification methods, and outcome assessments across reports, precluding robust meta-analytic conclusions. Furthermore, the lack of controlled epidemiological studies and standardized biomarkers for chronic infections impedes causal inference. These limitations underscore the need for multicenter prospective cohort studies with longitudinal follow-up to validate temporal relationships and quantify risk magnitudes. Future investigations should prioritize harmonized protocols integrating advanced neuroimaging, serological profiling, and genetic susceptibility analyses (eg, RNF213 variants) to disentangle infection-related mechanisms from idiopathic moyamoya pathology. The establishment of international registries capturing detailed infection histories, treatment responses, and long-term outcomes would significantly enhance evidence quality.

The potential link between infections and MMD underscores the importance of vigilance in clinical practice, particularly in genetically susceptible individuals (eg, those with RNF213 variants)[60] or pediatric patients with a history of infections like varicella-zoster[56] or tuberculosis.[48] Clinicians should consider infections as possible associations in unexplained cerebrovascular events and explore anti-inflammatory therapies in infection-associated cases, though cautiously, given the lack of robust evidence. For research, priority lies in elucidating causal mechanisms—such as immune dysregulation, molecular mimicry, or cytokine-mediated vascular injury—through longitudinal cohort studies and preclinical models. Identifying biomarkers to distinguish infection-associated MMD subtypes could refine prognostication and personalized treatment. Additionally, investigating immunomodulatory interventions may open therapeutic avenues, while genetic-environmental interaction studies[78] could clarify the "second hit" hypothesis.[79] Bridging these insights will advance both prevention strategies and targeted management of this complex disorder.

On this basis, the treatment and care of moyamoya disease, such as the care of mental symptoms related to moyamoya disease, can be shifted to etiology-mechanism-oriented integrated interventions. At the treatment level, immunomodulatory therapies (such as anti-IL-6R therapy) and mental symptom management need to be incorporated into a joint clinical pathway - for example, preferentially using atypical antipsychotics with little impact on cerebral blood flow (such

as quetiapine), combining cognitive behavioral therapy to relieve stress-induced cerebrovascular spasm, and constructing a safe environment through family collaborative care to reduce the risk of epileptic seizures, thereby reducing the conflicting risks of combined use of immunomodulatory and psychiatric drugs; At the research level, it is necessary to deeply explore the biomarkers of the neuroimmune-psychiatric axis (such as cerebrospinal fluid GFAP/NF-L and plasma IL-6/TNF-α profiles), establish their correlation models with the severity of mental symptoms, and rely on international registry studies (such as MOYAOMICS) to integrate neuroimaging and multi-omics data, so as to promote the evidence-based transformation of precision care decisions.

Conclusion

Moyamoya disease is a complex disorder resulting from the interaction between genetic susceptibility (particularly RNF213 variants) and environmental triggers, with infections potentially acting as "second hits" in its pathogenesis. Although existing studies have identified potential mechanisms such as infection-induced vascular inflammation, these are constrained by methodological limitations like retrospective designs and small sample sizes, lacking definitive causal evidence. Future research should involve prospective multicenter studies integrating serological screening, neuroimaging, and genetic analysis, mechanistic validation using CRISPR-engineered models, and attention to psychiatric care with clarification of relevant biomarkers. Long-term efforts should focus on translating findings into clinical practice, including vaccination programs for genetically susceptible populations against high-risk pathogens and multi-omics-guided combined immunomodulatory and revascularization therapies. Advancing moyamoya disease care urgently requires actionable collaboration across neurology, infectious diseases, and psychiatry, bridging the gap between etiological hypotheses and clinical outcomes through interdisciplinary research.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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