Review

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Moyamoya Disease: Current Knowledge and Future Directions

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Abstract: Background and Purpose: Moyamoya disease is a rare cerebrovascular disorder characterized by stenosis of the carotid arteries and the formation of collateral vessels at the base of the brain. While advances have been made in understanding its genetics, diagnostic criteria, and treatment strategies, further research is needed. The purpose of this literature review is to synthesize current knowledge on Moyamoya disease and identify areas for future study. **Materials and Methods:** A literature search of databases including PubMed, Embase, and Web of Science was conducted. Search terms included "Moyamoya disease" and related terms. Only English articles were reviewed, with no date restrictions. Relevant data was extracted and synthesized. Results: Key findings indicate that genetic factors such as RNF213 variants play an important role in disease susceptibility. Imaging modalities such as MRI and CT angiography are crucial for diagnosis. Surgical revascularization shows superior outcomes compared to medical management for ischemic and hemorrhagic presentations. However, optimal treatment for asymptomatic cases remains unclear. Neurocognitive and psychiatric sequelae can negatively impact quality of life. Promising research directions include investigating ethnic differences, developing biomarkers, and exploring novel therapeutics targeting molecular pathways. Conclusions: In summary, comprehension of Moyamoya disease has significantly progressed but gaps remain regarding treatment of certain populations and underlying mechanisms. Further research addressing these areas can aid in developing personalized care approaches and new interventions to improve patient outcomes.

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1. Introduction

Moyamoya disease is a rare cerebrovascular disorder characterized by the progressive narrowing of the internal carotid arteries, leading to the development of an abnormal network of blood vessels at the base of the brain. This condition, first described in Japan, presents a significant challenge in the realm of neurological health due to its potential to cause strokes, transient ischemic attacks, and cognitive decline [1]. Recent advancements in the understanding of Moyamoya disease have shed light on its underlying genetic factors, such as the RNF213 gene, which has been identified as a major susceptibility gene for this condition[2]. The identification of such genes has not only provided insights into the pathophysiology of the disease but has also opened new avenues for investigating potential treatment targets[2]. In addition to genetic factors, diagnostic criteria play a crucial role in the accurate identification and management of Moyamoya disease. The Research Committee on Moyamoya Disease has recently revised the diagnostic criteria to enhance their scientific basis and promote wider recognition in the medical community[3]. These updated criteria are vital for improving the early detection of Moyamoya disease and facilitating timely interventions to prevent severe neurological consequences. The management of Moyamoya disease is another critical aspect that requires careful consideration. Surgical revascularization has emerged as a beneficial approach for both ischemic and hemorrhagic patients with Moyamoya disease, showcasing

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superior outcomes compared to conservative management in certain cases [4]. However, the optimal treatment strategy for asymptomatic Moyamoya disease in adults remains a topic of ongoing research and debate [4]. Overall, the comprehension of Moyamoya disease has significantly evolved in recent years, with a growing emphasis on genetic susceptibility, diagnostic criteria, and treatment strategies. By combining insights from genetic studies[2], updated diagnostic criteria[3], and advancements in surgical management[4] , healthcare providers can enhance their understanding and approach to addressing Moyamoya disease, ultimately improving patient outcomes and quality of life.

2. Materials and Methods Literature Review

A comprehensive literature search was conducted to identify relevant publications on Moyamoya disease. The following electronic databases were searched: PubMed, Embase, Web of Science, Scopus, and Google Scholar. Search terms included various combinations of "Moyamoya disease", "moyamoya", and "moyamoya syndrome". The literature search was not limited by study design or publication type. Articles published in English language were considered. No date restrictions were placed on the searches to ensure all available evidence was captured. Additionally, reference lists of eligible studies were screened to identify further publications not indexed in the electronic databases.

3. Results and Discussion

3.1. Historical Background and Discovery

The historical insights into the discovery and understanding of Moyamoya disease have been a subject of interest for researchers across different disciplines. One significant historical milestone in this regard was the introduction of carotid angiography employing a percutaneous technique, which paved the way for further investigations into cerebrovascular diseases[5]. This technique, developed by Shimizu in the late 1950s and early 1960s, was crucial for the visualization of vascular abnormalities associated with Moyamoya disease. The images obtained through this technique helped in the identification of distinct pathophysiological features of Moyamoya disease, setting the stage for future research endeavors. As the diagnostic tools and techniques evolved, newer insights into the pathophysiology of Moyamoya disease emerged. Genetic studies, such as those focusing on single nucleotide polymorphisms (SNPs), have shed light on the genetic etiology of Moyamoya disease, offering a promising avenue for understanding the underlying mechanisms of the condition[6]. Additionally, the discovery of pathogenic variants in the DIAPH1 gene in non-East Asian individuals with sporadic Moyamoya disease has provided crucial insights into the molecular basis of the disease, highlighting the significance of impaired vascular cell actin remodeling in its pathogenesis[7]. Moreover, recent studies have delved into the molecular and cellular pathophysiology of Moyamoya disease, uncovering potential therapeutic targets for non-surgical interventions[8]. With a focus on various omic approaches, these investigations aim to identify biomarkers that could aid in the diagnosis and treatment of Moyamoya disease, ushering in a new era of precision medicine for this complex condition[9]. Furthermore, research has explored the effects of Moyamoya disease on cerebral cortical structure and cognitive function, revealing patterns of cortical complexity that correlate with cognitive dysfunction post-stroke in Moyamoya patients[10]. These findings underscore the intricate relationship between structural brain changes and cognitive impairments in individuals with Moyamoya disease, contributing to a deeper understanding of the neurological consequences of the condition.

3.2. Importance of Understanding the Disease due to Its Implications on Neurological Health

Understanding Moyamoya disease has significantly advanced with the identification of RNF213 as a key gene linked to the disease's susceptibility[2]. This finding has not only shed light on the underlying mechanisms of the disease but has also paved the way for exploring potential treatment targets. The pathophysiological aspects of vascular stenosis and remodeling in Moyamoya disease have been thoroughly reviewed, emphasizing various molecular pathways associated with cellular proliferation, migration, apoptosis, and inflammation[11] . Moreover, accumulating evidence

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supports the benefits of revascularization surgery over conservative management for adult Moyamoya disease patients, particularly those presenting with ischemic or hemorrhagic symptoms[12] . In the context of surgical interventions for Moyamoya disease, the superficial temporal artery to middle cerebral artery anastomosis remains a vital procedure for increasing substrate supply and reducing demand, reflecting the complexity of anesthetic management in this condition[13]. The progression of Moyamoya disease's pathophysiology involves intricate interactions between genetic, angiogenic, and inflammatory factors, contributing to vascular stenosis and abnormal angiogenesis[14]. Furthermore, recent research has identified the importance of cerebral angiography and endovascular treatments in managing Moyamoya disease, albeit with uncertainties regarding their long-term efficacy and suitability in different patient populations[15]. From a broader perspective, a bibliometric analysis has highlighted the most impactful articles on Moyamoya disease, offering insights into the current understanding of the condition and guiding future research endeavors[16]. Additionally, a scientific statement by the American Heart Association/American Stroke Association provides updated definitions, diagnostic methods, and treatment strategies for adult Moyamoya disease and syndrome, underscoring the importance of a multidisciplinary approach in managing these patients[17] .

4. Epidemiology and Risk Factors

4.1. Global Prevalence and Distribution Patterns

Despite Moyamoya disease's initial association with Japan and East Asian countries such as Korea, the worldwide distribution of Moyamoya disease remains unclear[18]. Notably, Moyamoya disease's prevalence is notably increasing globally, with distinct epidemiological patterns observed in different regions[19] [20]. However, some regions like Eastern India have shown unique gender predispositions, age distributions, and disease manifestations compared to their Japanese and Caucasian counterparts[19]. Such intercontinental differences emphasize the need for a comprehensive understanding of Moyamoya disease's worldwide burden and distribution patterns Moyamoya Disease Worldwide-Global Burden East and West[21]. High-resolution vessel wall imaging has been suggested as a valuable tool for aiding in the diagnosis and management of Moyamoya disease[22]Furthermore, the genetic landscape of Moyamoya disease has been explored, with studies identifying susceptibility genes associated with this disorder[23]. For instance, polymorphisms in MRVI1 have been linked to Moyamoya syndrome in European patients with neurofibromatosis type 1[23]. Additionally, genetic variations in RNF213 have been highlighted as important susceptibility factors for Moyamoya disease, particularly in East Asian countries [19]. Investigating infarction patterns in Moyamoya disease patients has revealed varying risks of recurrent adverse cerebrovascular events based on different patterns observed on diffusion-weighted imaging[24]. These findings underline the significance of paying attention to prevent such events in Moyamoya disease patients with specific infarction patterns.

4.2. Age and Gender Predilection & Genetic and Environmental Risk Factors

Several studies have delved into the specific demographic and genetic factors influencing Moyamoya disease susceptibility. A study by Kim et al [25]. highlighted the significance of the RNF213 polymorphism in Korean patients with Moyamoya disease, particularly the c.14429G>A (p.R4810K) allele, as a potential biomarker for early-onset or unstable Moyamoya disease with cerebral infarction. This genetic variant plays a crucial role in the clinical features and long-term outcomes of the disease. In another investigation by Mineharu et al[26], both genetic and non-genetic factors were found to be associated with contralateral progression in unilateral Moyamoya disease, shedding light on the pathophysiology of the condition and guiding better patient management strategies. Furthermore, the GEN-O-MA project in Italy, as outlined by Bersano et al[27], focuses on studying the clinical course and pathogenic pathways of Moyamoya disease. By collecting biological samples, the project aims to identify biomarkers and genetic factors related to disease susceptibility, ultimately enhancing the understanding of the disease phenotype and clinical progression. Moreover, Zhang et al[28]. investigated predictors of stroke outcomes in conservatively treated

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Moyamoya disease patients through a follow-up MRI study. They found that specific imaging characteristics and clinical parameters were associated with an increased incidence of stroke, emphasizing the importance of personalized treatment strategies for such individuals. The literature also includes insights from Hao et al[29], who explored the clinical and genetic risk factors linked to MRI vessel wall enhancement in Moyamoya disease, highlighting the strong association of the RNF213 p.R4810K variant with poor prognosis and the role of homocysteine and smoking as independent risk factors for vessel wall enhancement.

5. Pathophysiology

Understanding the underlying pathophysiology of Moyamoya disease is crucial for the development of effective treatment strategies. Several recent studies have shed light on the mechanisms contributing to vascular changes and impaired blood flow in Moyamoya disease. Recent research has highlighted the role of inflammatory processes in the pathophysiology of Moyamoya disease[30]. The review by Mikami et al. (2019) discusses the influence of inflammatory diseases on the pathophysiology of Moyamoya disease, providing novel insights for treatment approaches[30] This emphasizes the importance of considering inflammatory pathways in understanding the vascular changes observed in Moyamoya disease. Moreover, studies have explored molecular pathways involved in vascular stenosis and remodeling in Moyamoya disease[11] Fox et al. (2021) reviewed various molecular pathways implicated in the pathophysiology of stenosis in Moyamoya disease, including cellular proliferation, extracellular matrix remodeling, apoptosis, and vascular inflammation[11]. Understanding these pathways is crucial for unraveling the mechanisms contributing to the vascular changes observed in Moyamoya disease. Additionally, the study by Liu et al. (2022) identified the circZXDC–miR-125a-3p–ABCC6 axis as playing a pivotal role in the progression of Moyamoya disease[31]. This finding suggests a potential target for therapeutic interventions aimed at modulating vascular smooth muscle cell trans-differentiation in Moyamoya disease[31].

6. Clinical Presentation

6.1. Symptomatology across Different Age Groups

Moyamoya disease primarily manifests in two forms: ischemic, where patients experience symptoms related to reduced blood flow such as transient ischemic attacks and strokes, and hemorrhagic, where symptoms arise from blood vessel rupture causing bleeding in the brain[32]. As highlighted in various studies, the typical symptoms of Moyamoya disease can vary across different age groups, influencing the mode of presentation and management strategies [33]. In the pediatric population, Moyamoya disease has been associated with distinct clinical outcomes based on the initial symptoms. Choi et al. demonstrated that surgical intervention through encephaloduro-arteriosynangiosis was more effective in preventing epileptic seizures and improving clinical outcomes in pediatric patients presenting with seizures compared to those with cerebral ischemia[34] . On the other hand, Im et al. emphasized the role of direct and indirect bypass surgeries in alleviating involuntary movements induced by cerebral ischemia in pediatric patients, showcasing the effectiveness of surgical interventions in addressing specific symptoms related to reduced blood flow[35]. Furthermore, Moyamoya disease in adolescents presents a unique set of symptoms, with limb weakness being the most common followed by headache, difficulty in speech, and nausea/vomiting. Oh et al. conducted a cluster analysis to identify this diverse symptomatology, suggesting a multidimensional approach for symptom recognition and management in adolescent patients[36]. In adults, Moyamoya disease can present with atypical symptoms, as demonstrated in the case of a Hispanic woman with a history of diabetes and asthma who exhibited recurrent transient episodes of weakness and confusion[37]. This highlights the importance of considering non-typical risk factors and symptoms in the diagnosis and management of Moyamoya disease across different ethnicities and age groups.

6.2. Diagnostic Criteria and Imaging Modalities and Complications and Neurological Sequelae

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The primary diagnostic criteria for identifying Moyamoya disease have been recently revised in 2021 by the Research Committee on Moyamoya Disease[3]. These revised diagnostic criteria aim to enhance the understanding and recognition of Moyamoya disease on a global scale, reflecting the latest scientific advancements in the field. Imaging plays a crucial role in the diagnosis of Moyamoya disease, with various modalities being commonly utilized. To facilitate the diagnostic process, standardized imaging protocols have been established for preoperative and postoperative evaluation of Moyamoya disease and Moyamoya syndrome[38]. These imaging techniques play a significant role in the further advancement of the scientific knowledge surrounding Moyamoya disease and its management. Moreover, high-resolution magnetic resonance-vessel wall imaging has been explored as a potential tool to simplify the assessment of Moyamoya disease[39]. By focusing on variant vessel wall features, this advanced imaging modality could aid in differentiating Moyamoya disease and providing valuable insights into patient prognosis. The complications associated with Moyamoya disease can pose significant challenges in clinical management. For instance, headaches often persist or develop after revascularization surgery in pediatric Moyamoya disease patients, with distinct characteristics such as accompanying nausea or vomiting and occurrence upon awakening[40]. Understanding and effectively managing these complications are essential for optimizing patient outcomes postoperatively.

7. Treatment Strategies

7.1. Medical Management Options

When considering medical management options for individuals diagnosed with Moyamoya disease, it is essential to evaluate both the lack of evidence supporting pharmaceutical interventions[41] and the outcomes of surgical revascularization procedures(Gupta et al., 2021) [12]. Although drug treatments have not shown clear benefits in Moyamoya disease[41], surgical intervention, such as encephaloduroarteriosynangiosis procedures[43], has demonstrated positive outcomes, including a graft patency rate of 97%(Gupta et al., 2021). Moreover, the role of surgery is especially crucial for individuals with hemorrhagic Moyamoya disease, as it is recommended as the treatment of choice in such cases[44]. Furthermore, ongoing research emphasizes the importance of surgical interventions over conservative management, not only for ischemic patients but also for asymptomatic individuals with Moyamoya disease. Specifically, the encephaloduroarteriosynangiosis procedure has been highlighted as a form of indirect revascularization that can prevent further neurologic decline in patients with Moyamoya disease. Additionally, the development of cerebral microbleeds and their impact on cognitive function in adult patients receiving medical management alone for ischemic Moyamoya disease underscores the need for effective treatment strategies[41]. While the current literature lacks substantial evidence supporting the efficacy of drug therapy in Moyamoya disease[12], a comprehensive understanding of the pathogenesis of the disease, as well as potential therapeutic targets, can pave the way for future medical interventions[2]. Future research, such as the Moyamoya Omics Atlas project, aims to revolutionize the diagnosis, patient stratification, and the development of targeted therapies for Moyamoya disease [45].

7.2. Surgical Interventions: Revascularization Procedures

Surgical revascularization procedures play a crucial role in improving outcomes for Moyamoya patients. A study by Titsworth et al[46]. analyzed 2454 pediatric Moyamoya admissions and found that high-volume centers provide significantly improved care and reduced mortality, especially in cases requiring surgical revascularization. Moreover, Yuan et al[47]. conducted a study comparing the outcomes of different surgical revascularization procedures for adult Moyamoya disease. They found that STA-MCA yielded larger postoperative perfusion areas and greater improvements, suggesting the potential of computed tomography perfusion in elucidating variations in symptoms between procedures. In a case report by Almutairi et al[48]. Moyamoya disease was identified as the cause of sudden neurological symptoms in an adult female. The case underscored the importance of considering Moyamoya disease in the differential diagnosis of such patients. Furthermore, Zhang et

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al[49] demonstrated that combined revascularization was superior to indirect revascularization alone in preventing long-term rebleeding in adult hemorrhagic moyamoya disease patients. Wang et al[50] compared indirect revascularization with non-surgical treatments for Moyamoya disease and found that surgery significantly reduced the recurrent stroke incidence in patients. Additionally, a study by Wali et al[51] analyzed the cost-effectiveness of surgical revascularization for Moyamoya disease in the United States and concluded that surgery is considerably more cost-effective than non-surgical management for adults with Moyamoya disease.

7.3. Emerging Therapies and Potential Future Directions

As researchers delve into understanding its etiology and pathophysiology, emerging therapies and research directions are offering new hope for its treatment[52]. Advanced imaging techniques and genetic studies are shedding light on the disease's mechanisms, suggesting potential targets for therapy[6]. Furthermore, the exploration of immune-related responses as triggers for Moyamoya disease onset highlights novel directions for therapeutic interventions[53]. In the quest for improved treatments, the field is also investigating the impact of revascularization techniques on the neuropsychological outcomes of Moyamoya disease patients[54]. Understanding the broader neuropsychiatric sequelae associated with the condition brings attention to the holistic care required for individuals affected by Moyamoya disease[55] Additionally, genetic and proteomic contributions to the pathophysiology of Moyamoya angiopathy offer promising avenues for new interventions[56] . As the landscape of Moyamoya disease research continues to evolve, collaborations between clinical practitioners and researchers are essential for developing comprehensive guidelines and approaches to tackle this challenging condition [57] By integrating cutting-edge imaging methods, genetic insights, and a deep understanding of both the disease's physiological underpinnings and its broader impact, the field is poised to revolutionize Moyamoya disease treatment and management.

8. Quality of Life and Prognosis

8.1. Impact on Cognitive Function and Daily Activities

Research has shown that cognitive impairment may precede the onset of clinical symptoms such as cerebral infarction in asymptomatic Moyamoya disease (MMD) patients[58]. White matter hyperintensities (WMH) burden has been found to be highly correlated with global cognition, memory, semantic memory, and executive function in asymptomatic MMD patients, highlighting the cognitive impact of this condition[59]. Additionally, cognitive impairment has been linked to hypoperfusion in specific brain regions, emphasizing the importance of cerebral hemodynamics in cognitive function in MMD patients[60]. Moreover, a study on postoperative executive function in adult Moyamoya disease patients revealed that improvements in cognitive function after surgery are associated with postoperative recovery in the binding potential of central benzodiazepine receptors in the affected cerebral hemisphere, indicating the potential for cognitive enhancement with surgical interventions. Furthermore, a predictive model has been developed to assess the risk of decreased living activity ability in patients with MMD, enhancing our ability to anticipate and manage functional decline in these individuals[61]. The impact of Moyamoya disease on cognitive function has also been explored longitudinally, with findings indicating that specific cognitive domains can decline over time in patients with adult Moyamoya disease[62]. Preoperative resting-state functional connectivity has shown promise in predicting post-surgical longitudinal neurocognitive changes in MMD patients, pointing towards potential personalized treatment approaches based on brain connectomics[63].

8.2. Long-Term Outcomes and Factors Influencing Prognosis and Challenges in Managing the Disease and Improving Patient Outcomes

Understanding the factors influencing the quality of life and prognosis of Moyamoya disease patients is crucial for improving patient outcomes. Research has shown that Moyamoya disease can have neuropsychiatric sequelae, impacting cognitive function, psychiatric well-being, and overall quality of life. Moreover, long-term outcomes vary between patients with and without

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revascularization, with the prognostic nutrition index being identified as a potential predictor for unfavorable outcomes after revascularization[64]. This emphasizes the need for a comprehensive approach in managing Moyamoya disease to enhance patient well-being and prognosis. Patients with Moyamoya disease face unique challenges that affect their quality of life and long-term outcomes. It has been observed that conservative treatment of adult patients may lead to a higher risk of stroke, particularly hemorrhagic stroke, indicating the need for additional strategies to prevent adverse outcomes in this population[65] . On the other hand, patients with both Moyamoya disease and atherosclerosis-associated vasculopathy could benefit from treatments such as encephaloduroarteriosynangiosis, as identified through high-resolution MR vessel wall imaging[66]. This highlights the importance of personalized interventions based on the specific characteristics of the disease in each patient. In the context of other chronic diseases, studies have investigated the impact of various factors on the quality of life and long-term outcomes. For instance, in patients with chronic kidney disease undergoing renal replacement therapy, functional status was found to be a strong predictor of patient-reported outcomes[67]. Similarly, individuals with lower extremity peripheral artery disease experienced poor quality of life, especially concerning physical components, indicating the need for targeted management strategies[68]. Furthermore, factors such as satisfaction with treatment and follow-up care have been associated with changes in health-related quality of life in individuals receiving long-term mechanical ventilation[69].

9. Research Advances and Future Directions

9.1. Recent Developments in Understanding the Disease Mechanisms

Recent advances in Moyamoya disease research have significantly deepened our understanding of this complex condition. One of the pivotal developments is the revised diagnostic criteria for Moyamoya disease in 2021, meticulously described by Fujimura et al.[70]. This publication sheds light on the scientific basis underlying the new criteria, aiming to disseminate this crucial information globally. Moreover, the 2021 Japanese Guidelines for the Management of Moyamoya Disease offer essential insights into the best practices in treating this condition[71]. These guidelines, formulated by Fujimura et al., provide valuable recommendations from the Research Committee on Moyamoya Disease and the Japan Stroke Society. Moreover, Iwaki et al. introduced a groundbreaking hyperspectral imaging system that shows promise in predicting postoperative cerebral hyper-perfusion syndrome in Moyamoya disease patients[72]. By analyzing the cortical tissue, this innovation could revolutionize the way postoperative complications are anticipated and managed. Additionally, Kang et al. successfully isolated smooth-muscle progenitor cells from Moyamoya disease patients, creating a novel experimental cell model for further research[73]. This innovative approach opens new avenues for studying the disease at a cellular level and understanding its pathophysiology better. Furthermore, Arias et al. comprehensively reviewed various aspects of Moyamoya disease, including its clinical characteristics, underlying pathology, surgical techniques, and patient outcomes[70].

9.2. Current Gaps in Knowledge and Areas for Further Investigation

The literature surrounding Moyamoya disease offers valuable insights into its management, etiology, and treatment options. One significant contribution to the field is the 2021 Japanese Guidelines for the Management of Moyamoya Disease, a collaborative effort by the Research Committee on Moyamoya Disease and the Japan Stroke Society[70]. These guidelines provide a comprehensive framework for addressing the complexities of Moyamoya disease management, offering clinical insights that can guide future research directions. Gupta et al. (2020) conducted a critical analysis of current literature on Moyamoya disease, shedding light on key aspects such as etiology, diagnosis, and treatment[74]. This review underscores the importance of continuously updating our understanding and approaches to managing this challenging condition. On the genetic front, Hara et al. (2022) delved into the RNF213 gene variants in Moyamoya disease, pointing out remaining unanswered questions in this genetic aspect of the disease[75]. Understanding the genetic underpinnings of Moyamoya disease is crucial for developing personalized treatment approaches,

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potentially leading to advancements in precision medicine[76]. Furthermore, investigating pediatric Moyamoya arteriopathy has revealed genotype-phenotype correlations that highlight the need for tailored management strategies for different patient groups[77]. Addressing these correlations and understanding the distinct clinical features of patients with specific genetic profiles could pave the way for more targeted and effective treatments. Despite the progress in Moyamoya disease research, gaps persist, particularly concerning the role of ethnicity in prognosis and the need for more diverse clinical data[78]. Future studies should aim to address these knowledge gaps to improve our understanding and management of Moyamoya disease comprehensively.

9.3. Promising Avenues for Therapeutic Interventions and Prevention Strategies

Ongoing research efforts aim to enhance therapeutic interventions and preventives strategies for Moyamoya disease. The discovery of the major susceptibility gene RNF213 has opened new avenues for investigating the disease mechanisms[2]. Studies have suggested that the pathophysiology of Moyamoya disease can be influenced by inflammatory diseases, providing novel insights for potential treatments[30]. An updated review on Moyamoya disease diagnosis and treatments emphasizes the importance of considering controversial issues in the disease management[79]. Moreover, current research has proposed utilizing multiomics and blood-based biomarkers to revolutionize early diagnosis and targeted therapies for Moyamoya disease[45]. In the context of neurodegenerative diseases, such as Alzheimer's, novel therapeutic approaches have been explored focusing on anti-amyloid therapy, anti-tau therapy, and neuroprotective agents, indicating potential strategies that could be adapted for Moyamoya disease[80]. Dysregulation in the endosomal-lysosomal system has been linked to the pathogenesis of neurodegenerative diseases, suggesting that understanding these dysfunctions could lead to new therapeutic interventions[81]. Moreover, research on Moyamoya disease's pathogenesis has proposed the "double hit hypothesis" as the best explanation for the disease's complexities, highlighting the significance of continuous investigations to identify effective treatment strategies[82]. The proposal for a prospective registry for Moyamoya disease in Japan aims to provide critical insights into patient management and develop improved therapies through detailed statistics and patient stratification[83]. Therefore, by leveraging insights from genetic susceptibility, pathophysiology, inflammation influence, and novel therapeutic approaches from related fields like neurodegenerative diseases, ongoing research efforts hold the promise of advancing therapeutic interventions and preventive strategies for Moyamoya disease.

Conclusions

In summary, comprehension of Moyamoya disease has significantly progressed but gaps remain regarding treatment of certain populations and underlying mechanisms. Further research addressing these areas can aid in developing personalized care approaches and new interventions to improve patient outcomes.

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