Scientific Research Publishing

World Journal of Neuroscience, 2024, 14, 6-23
https://www.scirp.org/journal/wjns
ISSN Online: 2162-2019
ISSN Print: 2162-2000

Recent Advances for Global Perspectives on Etiology, Pathophysiology, Clinical Presentations, and Management of Moyamoya Disease

Maiko Charles Mkwambe, Dongchi Zhao*, Youping Deng*

Department of Pediatrics, Zhongnan Hospital of Wuhan University, Wuhan, China
Email: *zhao_wh2004@hotmail.com, *dengyp@whu.edu.cn

How to cite this paper: Mkwambe, M.C., Zhao, D.C. and Deng, Y.P. (2024) Recent Advances for Global Perspectives on Etiology, Pathophysiology, Clinical Presentations, and Management of Moyamoya Disease. *World Journal of Neuroscience*, **14**, 6-23.
https://doi.org/10.4236/wjns.2024.141002

Received: November 16, 2023
Accepted: February 5, 2024
Published: February 8, 2024

Abstract

Moyamoya disease (MMD) is a condition characterized by the gradual narrowing and blockage of blood vessels in the brain, specifically those in the circle of Willis and the arteries that supply it. This results in reduced blood flow and oxygen to the brain, leading to progressive symptoms and potential complications. The underlying pathophysiological mechanism remains elucidated. However, recent studies have highlighted numerous etiologic factors: abnormal immune complex responses, susceptibility genes, branched-chain amino acids, antibodies, heritable diseases, and acquired diseases, which may be the great potential triggers for the development of moyamoya disease. Its clinical presentation has varying degrees from transient asymptomatic events to significant neurological deficits. Moyamoya disease (MMD) shows different patterns in children and adults. Children with MMD are more susceptible to ischemic events due to decreased blood flow to the brain. Conversely, adults with MMD are more prone to hemorrhagic events involving brain bleeding. Children with MMD may experience a range of symptoms including motor impairments, sensory issues, seizures, headaches, dizziness, cognitive delays, or ongoing neurological problems. Although adults may present with similar clinical symptoms as children, they are more prone to experiencing sudden onset intraventricular, subarachnoid, or intracerebral hemorrhages. One of the challenges in moyamoya disease is the potential for misdiagnosis or delayed diagnosis, particularly when physicians fail to consider MMD as a possible cause in stroke patients. This review aims to provide a comprehensive overview of recent global studies on the pathophysiology of MMD, along with advancements in its management. Additionally, the review will delve into various surgical treatment options for MMD, as well as its rare

*Corresponding authors.

occurrence alongside atrioventricular malformations. Exciting prospects include the use of autologous bone marrow transplant and the potential role of Connexin 43 protein treatment in the development of moyamoya disease.

Keywords

Moyamoya Disease (MMD), Etiology, Pathophysiology, Clinical Presentations, Management, Future Promising Avenues

1. Introduction

Moyamoya disease (MMD) is a condition marked by the progressive narrowing of the internal carotid artery and circle of Willis, leading to chronic bilateral vasculopathy. The exact cause of MMD is unknown. In contrast, moyamoya syndrome (MMS) is characterized by the occurrence of the same phenomenon in conjunction with other neurological or extra-neurological conditions, which can be either inherited or acquired [1] [2]. People diagnosed with Moyamoya disease (MMD) have a higher likelihood of experiencing stroke, cognitive difficulties, and delays in their development. Collateral vessels, known as moyamoya vessels, develop in response to chronic brain ischemia. Recent research has identified several susceptibility genes, including individuals diagnosed with familial moyamoya disease, that have the 95% p. R4810K variant in the RNF213 gene [3]. Studies have found that Moyamoya disease is more common in individuals of Asian descent, with a higher prevalence observed in Japan where the condition was first discovered [4]. Interestingly, MMD is linked to have an association with mutations in human RNF213 and ACTA2 genes. MMD has a bimodal distribution, with peaks between the ages of 5 to 10 years in children and then between ages 30 - 50 years in adults; the population of patients from the second peak is smaller than the first. MMD has a family history, which is positive in 10% - 15% of patients with initial onset followed by slow progression [4] [5]. According to a prospective study involving 23 patients diagnosed with ischemic MMD using DSA, it was discovered that TGFβ1 is crucial in facilitating the development of collateral blood vessels by increasing the expression of VEGF in ischemic MMD. Comparatively higher levels of TGFβ1 were observed in the plasma of ischemic MMD patients when compared to individuals with aneurysms and those who are in good health. This finding led to the conclusion that TGFβ1 plays a significant role in promoting collateral formation in ischemic MMD [6]. Cerebral angiography has played a critical role in the diagnosis and grading of MMD. The presence of "a puff of smoke" or moyamoya vessels, observed through catheter angiography at the base of the brain, is considered the characteristic feature that is specific to MMD [7]. Cerebral angiography carries the risk of complications, including brain ischemia and vascular damage, with reported incidences of 2.9% - 9.3%. This risk is particularly higher in pediatric patients and those with MMD who have significant hemodynamic compromise

[8]. A case-control study conducted between September 2020 and December 2021 found that elevated levels of circulating BCAAs were linked to a higher risk of MMD and its various clinical subtypes in a group of 360 adults with MMD and 89 healthy controls [9]. But, advancements in high-throughput multi-omics technologies have provided new insights into the origins of diseases [10]. MMD encompasses both ischemic and hemorrhagic blood types, with ischemic MMD being more common in children and cerebral hemorrhage being predominantly observed in adults. The mortality rate of hemorrhagic MMD is reported to be higher compared to ischemic MMD [11]. Henceforth, objective of this review is to explore the lesser-known causes of moyamoya disease, focusing on recent advancements in understanding its pathophysiology, available treatment options, and potential future directions in this era of significant scientific breakthroughs.

2. Etiology of Moyamoya Disease

2.1. Genetic Predisposition

Moyamoya disease has been widely accepted that it has a genetic component, with specific gene mutations with approximately 10% of patients identified in familial cases. Mineharu proposed that familial moyamoya disease follows an autosomal dominant inheritance pattern, characterized by incomplete penetrance that is influenced by factors such as age and genomic imprinting [12]. Through a comprehensive analysis of the entire genome, a study on moyamoya disease (MMD) successfully identified RNF213 as the initial gene linked to this condition [13]. On the other hand, another study found that, mutations in RNF213 may disrupt normal vascular development and lead to abnormal angiogenesis, resulting in the characteristic narrowing of blood vessels in moyamoya disease [14]. In a notable genome-wide association study conducted by Duan *et al.* in China, they discovered ten previously unidentified risk loci, alongside RNF213, that have significant genetic implications for moyamoya disease (MMD). Two of these newly identified risk genes, MTHFR and TCN2, play a role in the metabolism of homocysteine, which is a recognized risk factor for coronary heart disease and stroke. These genes have an impact on endothelial function and angiogenesis, further highlighting their relevance in MMD [14]. However, individuals who carry the RNF213 p. (R4810K) gene mutation, both in homozygous and heterozygous states, have been found to have arteriopathies in various arteries such as the coronary, renal, celiac, mesenteric, and iliac arteries. This discovery suggests the importance of conducting systematic screenings for extracranial vasculopathy in both adult and pediatric patients with moyamoya disease (MMD) [15].

2.2. The Role of Inflammatory Cytokines

The presence of extracranial vasculopathy in individuals with moyamoya disease (MMD) is not limited to the R4810K gene variant. This is evidenced by the recent discovery of a new clinical syndrome characterized by childhood-onset MMD with diffuse occlusive vasculopathy [16]. A recent discovery has linked a

specific genetic mutation to the development of urticarial lesions, which are accompanied by elevated levels of inflammatory cytokines. These cytokines, such as IL-1β, tumor necrosis factor alpha, and IL-6, mimic the symptoms of an acute cytokine storm. This finding emphasizes the importance of RNF213 as a key inflammatory mediator and a significant factor in the development of moyamoya disease (MMD) [17]. Moyamoya disease (MMD) is linked to Down syndrome, sickle cell disease, cancer, and exposure to radiation.

2.3. Autoimmune Conditions

Autoimmune conditions, such as systemic lupus erythematosus (SLE) and thyroid disease, have been associated with moyamoya disease. Autoimmune mechanisms may contribute to the vascular inflammation and narrowing observed in moyamoya disease. Autoimmune responses targeting vascular endothelial cells or components of the blood-brain barrier may lead to vascular dysfunction and the development of moyamoya disease [18] [19].

Additionally, studies suggest that autoimmune conditions and infection may also contribute to the development of MMD [20]. Graves' disease, a thyroid disorder, has been found to progress more rapidly in patients with moyamoya disease (MMD). These patients also have a higher incidence of stroke. This suggests that Graves' disease is an independent factor in the progression of MMD in adult patients, indicating shared underlying mechanisms between the two conditions and other autoimmune diseases [21].

2.4. The Role of Bacterial Infections

Additionally, complications of progressive arterial occlusive disease have been observed in patients following purulent meningitis. This condition can be caused by various pathogens such as Hemophilus influenzae, Streptococcus pneumoniae, Mycobacterium tuberculosis, and Leptospira. These complications typically develop around two weeks after the onset of the disease and are characterized by a progressive nature. Late-onset morphologic changes in the circle of Willis are also observed [22]. Moyamoya disease (MMD) can occur following viral infections associated with certain arteriopathies like transient cerebral arteriopathy (TIA) and progressive arteriopathies. These infections can contribute to the development of moyamoya angiopathy (MMA) [23]. Post-infectious vasculopathy may be due to an autoimmune response triggered by infection, involving β2-GP1 and post-infectious antiphospholipid syndrome. This could explain an abnormal immune response to viral infection, leading to an increased vulnerability to moyamoya disease [24].

2.5. Viral Infections

Viral infections have been implicated in the development of moyamoya disease. Emerging evidence suggests a link between viral-associated Moyamoya disease (MMD) and COVID-19 caused by SARS-CoV-2. COVID-19 patients with increased blood clotting may also have effects on RNF213 and caveolin-1 due to

the cytokine storm associated with the virus [25] [26]. Other studies have found that, viruses such as human herpesvirus 6 (HHV-6) and varicella-zoster virus (VZV) have been detected in the blood vessels of moyamoya disease patients. It is hypothesized that viral infections may trigger an immune response and subsequent inflammation in the blood vessels, leading to stenosis and the development of moyamoya disease [27] [28].

3. Pathophysiology of Moyamoya Disease

Moyamoya disease (MMD) is a condition where the inner layer of the walls of the internal carotid vessels, especially in their end segments, becomes thickened. This thickening may contain lipid deposits. The arteries branching from the circle of Willis, like the anterior, middle, and posterior cerebral arteries, can become narrowed or blocked to varying degrees. This narrowing is associated with the thickening of the inner artery walls, the waving of a specific elastic layer, and the thinning of the middle layer. Within the circle of Willis, there are small channels known as perforators and anastomotic branches that facilitate vascular connections. The pia mater, a thin membrane covering the brain, may also have clusters of small vessels.

Figure 1 illustrates the continuous blockage of major brain arteries, specifically the internal carotid arteries and their branches. This blockage is caused by the increased presence of growth factors such as VEGF (Vascular endothelial growth factor), TGF (transforming growth factor), HGF (Hepatocyte growth factor), MMPs (Matrix metallopeptidases), and bFGF (basic fibroblast growth factor) in the brain tissue. These growth factors promote the formation of new blood vessels, known as collateral vessels, which serve as a compensatory mechanism to bypass the narrowed or blocked arteries. However, these collateral vessels are fragile and susceptible to rupture, resulting in brain hemorrhage and an elevated risk of stroke.

Although the exact cause of MMD is not fully understood, several studies have identified various factors that may contribute to its development. Specific gene mutations can contribute to the development of Moyamoya disease (MMD), Moyamoya syndrome (MMS), and cerebral arteriopathies. For instance, autosomal recessive MMD with achalasia is associated with mutations in the GUCY1A3 gene, which plays a role in nitric oxide signaling. Mutations in the ACTA2 gene, specifically heterozygous missense mutations, can cause a condition that exhibits similarities to Moyamoya disease. These mutations affect the production of smooth muscle actin. Mutations in the SAMHD1 gene can cause an inflammatory syndrome accompanied by moyamoya-like vasculopathy. X-linked MMS with short stature and facial dysmorphism is linked to deletions in the BRCC3 gene on the X chromosome. Additionally, de novo mutations in the CBL gene, involved in protein degradation, can result in severe early-onset pediatric moyamoya arteriopathy [28]-[33]. The narrowing of blood vessels in Moyamoya disease is thought to lead to chronic brain ischemia, causing an

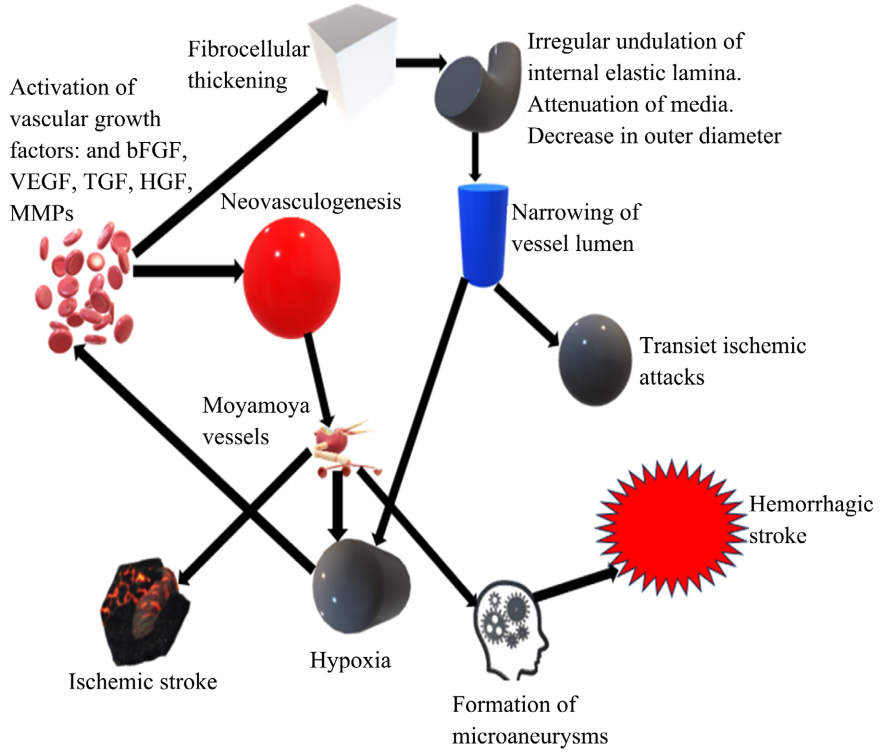

Figure 1. Pathophysiology of Moyamoya disease.

increase in the production of proangiogenic factors such as fibroblast growth factor and hepatocyte growth factor. This overexpression of proangiogenic factors is believed to stimulate the formation of a delicate network of collateral vessels [1] [34]. A study by Junsheng Li *et al.* found that Methionine sulfoxide (MetO) is linked to a higher risk of Moyamoya disease (MMD) and its subtypes. However, betaine has shown promise in reducing inflammation and oxidative stress following brain ischemia and reperfusion injury. This is achieved by increasing the levels of MetO reductase. The study also noted that MetO can inhibit the cleavage of ADAMTS-13, which can contribute to thrombosis in oxidative stress-related diseases [35]. Hemoglobin (Hb) and triglycerides (TG) have been found to play a role in the development of Moyamoya disease (MMD). Higher levels of Hb are linked to inflammation and increased risk of stroke and poor prognosis. Elevated TG levels also contribute to the risk of cerebrovascular diseases, such as artery stenosis. Early prevention of hyperuricemia and lipid abnormalities has been shown to decrease the occurrence of MMD. However, the exact connection between Hb and TG in the pathology of MMD is not fully understood [36]. Shifu Li *et al.*'s study revealed that molecular biology and next-generation sequencing technologies have improved our understanding of disease mechanisms at the genetic and mRNA levels. This includes identifying differentially expressed genes (DEGs) and immune complexes. The study also found that gene-miRNA interactions play a role in modifying protein expression during disease progression by targeting specific factors [37].

4. Clinical Presentation of Moyamoya Disease

Moyamoya disease (MMD) presents differently in children and adults. Children typically exhibit symptoms such as hemiparesis, sensory impairments, seizures, headaches, and mental deficits. In contrast, adults with MMD often experience sudden intraventricular or subarachnoid hemorrhage, along with similar symptoms to children.

5. Diagnostic Evaluations of Moyamoya Disease

5.1. Laboratory Evaluation

Evaluating hypercoagulability profiles is important for both pediatric and adult patients with Moyamoya disease. These profiles consist of various markers, including protein C, protein S, antithrombin III, homocysteine, factor V Leiden, erythrocyte sedimentation rate (ESR), thyroid function, and thyroid antibody levels. Studies have indicated that these markers are frequently elevated in individuals with moyamoya disease. One possible explanation is that the elevation of proinflammatory and angiogenic cytokines stimulates the production of growth factor-β and basic fibroblast growth factor. This ultimately leads to the formation of new blood vessels and angiogenesis. Additionally, both microangiopathic and macroangiopathic changes contribute to the development of ischemic symptoms in Moya-Moya syndrome [38].

5.2. Imaging Evaluations

Various imaging techniques have been investigated, but brain angiogram remains the gold standard for diagnosing Moyamoya disease [1] [39].

5.3. Conventional Cerebral Angiography

Study found blockages in the internal carotid artery or the anterior/middle cerebral arteries, accompanied by abnormal blood vessel networks. The condition is usually bilateral, but unilateral involvement can occur in some patients [39]. Studies have found that most patients had moderate to severe grades of disease, with only a small percentage having milder grades. Among the patients with atypical symptoms, the majority had moderate to severe disease. In a small percentage of patients, angiography showed a small superficial temporal artery, resulting in changes to surgical plans and the use of indirect bypass alone [40] [41]. Angiographic findings in moyamoya disease include:

Basal Collateral Vessels: Moyamoya disease is often associated with the development of basal collateral vessels, also known as moyamoya vessels, at the base of the brain. These vessels arise from the external carotid artery system and provide compensatory blood flow to the affected areas.

String of Beads Sign: On angiography, a characteristic finding in moyamoya disease is the "string of beads" appearance of collateral vessels. This sign refers to the alternating areas of stenosis and dilation along the course of the basal colla-

teral vessels.

Moyamoya Phenomenon: In addition to the characteristic angiographic findings in moyamoya disease, a similar pattern of collateral vessel formation can also be observed in other conditions, known as the moyamoya phenomenon. The moyamoya phenomenon can occur secondary to various underlying conditions, such as sickle cell disease, neurofibromatosis type 1, and radiation therapy [40] [41].

5.4. Magnetic Resonance Imaging (MRI)

MRI scans are valuable for identifying hemorrhages and strokes in the brain. When using FLAIR and T2 weighted sequences, old ischemic lesions appear as bright areas in the white matter, typically found in the distal vasculature or border zone areas. The FLAIR sequence can also reveal linear bright areas that indicate slowed blood flow and follow the brain's grooves, referred to as the "ivy" sign [42].

5.5. Cerebral Perfusion Measurement

Various imaging techniques, such as CTP, SPECT, MRI, xenon-enhanced CT, PET scan, and arterial spin labeling, are used in these evaluations. These methods typically show increased oxygen extraction, decreased overall blood flow in the brain with a focus on the posterior cerebral region, and impaired blood vessel response to carbon dioxide and acetazolamide in the area supplied by the internal carotid artery. These findings suggest a limited ability to regulate blood flow in the brain, known as low cerebrovascular reserve [43] [44] [45] [46].

5.6. Transcranial Doppler (TCD)

TCD has shown clinical utility in assessing disease progression and treatment response in patients with Moyamoya disease.

Disease Progression: TCD can provide valuable information about the progression of Moyamoya disease by measuring blood flow velocities in the affected vessels. Progressive stenosis or occlusion of the internal carotid arteries and their branches can be detected by increased blood flow velocities in the collateral vessels. TCD can monitor changes in blood flow velocities over time, helping to identify disease progression and guide treatment decisions.

Treatment Response: TCD can be used to evaluate the hemodynamic changes following surgical or endovascular revascularization procedures in Moyamoya disease. Postoperative TCD can assess the improvement in blood flow velocities and the establishment of collateral circulation. TCD findings can help determine the effectiveness of revascularization procedures and guide further management.

Monitoring Collateral Circulation: TCD can assess the development and function of collateral circulation in patients with Moyamoya disease. By measuring blood flow velocities in the collateral vessels, TCD can provide information about the adequacy of collateral circulation and its contribution to cerebral per-

fusion [47] [48].

5.7. Electroencephalography (EEG)

Seizures and their abnormal patterns are frequently observed in pediatric patients with MMD. EEG can help differentiate between different transient neurological events in MMD. The 'Rebuild-up' phenomenon, seen in about half of moyamoya patients, involves the reappearance of slow waves with higher amplitudes following hyperventilation and is not found in other conditions. This phenomenon indicates reduced blood flow. In a study by Jia Lu *et al.*, abnormal EEG patterns were found in 93.3% of cases, with focal slowing being the most common (80.0%), followed by epileptiform discharge (66.7%) and diffuse slowing (60.0%) [49].

5.8. Magnetic Resonance Angiography (MRA)

This is a reliable examination for assessing cerebral arteries and determining the degree of narrowing and collateral circulation around steno-occlusive lesions. In adults, the existence of a one-sided obstructive condition is classified as "Probable moyamoya", while bilateral occlusion in adults or unilateral occlusion in children is classified as "Definite moyamoya". This classification is due to the high likelihood of unilateral occlusion progressing to bilateral occlusion in children. It is worth noting that posterior circulation is usually unaffected in MMD, but it can be involved in Moyamoya syndrome [50] [51].

6. Clinical Staging of Moyamoya Disease

Currently, Suzuki staging is the preferred clinical guide for staging MMD. The stages of MMD according to Suzuki staging are as follows:

Stage 1: Stenosis or constriction occurring solely at the end segment of the internal carotid artery, as observed through angiography.

Stage 2: The occurrence of stenosis in the smaller branches at the end of the internal carotid artery, accompanied by the presence of deep moyamoya vessels, as observed through angiography.

Stage 3: The increased visibility and prominence of deep moyamoya vessels observed during angiographic examination. At this stage, MRA imaging may show a distinct "puff of smoke" appearance. Additionally, the bending or deviation of the anterior cerebral artery (ACA) and middle cerebral arteries (MCA) can also be observed.

Stage 4: Is the decrease of moyamoya syndrome describing the decrease in visibility and prominence of deep moyamoya vessels seen during angiographic examination. This stage is characterized by the emergence of transdural collaterals and the bending or deviation of the posterior cerebral artery (PCA).

Stage 5: "Diminishment of moyamoya", the continuous decline in the visibility and significance of deep moyamoya vessels seen during angiographic exams. As these progress, there is a further decrease in the presence of these vessels,

while transdural collateral vessels continue to develop and become more prominent.

Stage 6: "The fading away of moyamoya", the absence of profound moyamoya vessels seen in angiographic exams, along with complete blockage of the internal carotid artery (ICA). Consequently, the external carotid artery primarily supplies blood to the regions of the anterior cerebral artery (ACA) and middle cerebral artery (MCA) [1].

7. Treatment Options for Moyamoya Disease

7.1. Conservative Management

The primary objective in managing Moyamoya disease is to maintain cerebral blood flow and prevent additional strokes resulting from the gradual formation of blood clots. Aspirin is often prescribed to prevent strokes in moyamoya patients, despite limited evidence of its direct benefits. Many neurologists still recommend its use due to its potential to reduce the risk of future strokes, considering other risk factors. Aspirin is also used as a long-term therapy to prevent blood clot formation. The recommended dosage generally falls between 50 and 100 mg [52] [53]. Yuki Hamada *et al.* found ivy signs on imaging scans of a 67-year-old patient with moyamoya disease which were associated with an increase in the size of cerebral infarction but disappeared once the ischemia resolved, suggesting changes in blood flow. Interestingly, the patient had a favorable outcome without the need for antithrombotic therapy. This emphasizes the significance of considering multiple factors, including the patient's anatomical background and the severity of ischemia, when managing moyamoya disease during the acute phase [54]. However, in a study by Jae Youn Kim *et al.*, it was found that cilostazol led to larger outer diameters and less severe narrowing compared to other treatment groups. When considering clinical and genetic factors, it was determined that only the use of cilostazol was independently linked to negative remodeling after treatment [55].

7.2. Surgical Management

The most effective treatment for Moyamoya disease (MMD) is recommended when there is a decline in cerebral hemodynamics. Surgery is especially beneficial for children due to the rapid progression typically seen in the pediatric form of MMD [56]. There are multiple bypass techniques available for revascularization in Moyamoya disease (MMD). The choice of technique depends on factors like the patient's age, preoperative hemodynamics, neurological condition, and the specific areas in need of revascularization and at higher risk [57]. Encephalomyo spongiosis (EMS) and encephalo-duro-arterio spongiosis (EDAS) are procedures that use different arteries as blood supply sources. Various techniques, such as EMAS, EDAMS, and EGS, are used for different cases of Moyamoya disease. In situations where the posterior circulation is affected, the occipital artery can be employed as an indirect bypass [58]. Yixuan *et al.* found that

indirect revascularization surgery using the superficial temporal artery (STA) as the bypass vessel resulted in a rapid and short mean transit time (MTT) before and after the procedure. Although there was no statistical difference between subgroups, the study suggests that this surgery can effectively decrease the risk of recurrent stroke in patients with both Moyamoya disease (MMD) and Moyamoya syndrome (MMS) [59]. Sanjeev A Sreenivasan et al's study found a minimal occurrence of perioperative stroke and reversible transient ischemic attack (TIA). Additionally, it was interesting to note that 87% of patients experienced symptomatic improvement after undergoing the procedure [60]. Ultimately, Xiang-Yang Bao et al's study found that indirect reconstruction is a better approach for improving blood supply in ischemic areas of the brain compared to direct revascularization. Indirect reconstruction provides more stable and long-lasting benefits, while direct revascularization only offers temporary relief. The blood supply formed through indirect reconstruction is based on the severity of ischemia, allowing for a natural and balanced distribution of blood to different areas. It typically takes several weeks or even months for new collateral circulation to develop after indirect revascularization [61].

7.3. Direct Revascularization

In this surgical approach, the external temporal artery is used as the primary vascular circulation for arterial bypass surgery. It leads to immediate improvement in cerebral blood flow but requires a skilled surgeon. A study by Feng Gao *et al.* found similar Glasgow Coma Scale (GCS) scores after surgery in both groups. However, there were notable differences in clinical effectiveness and overall success rate. Both groups showed improvement in modified Rankin Scale (mRS) scores and Karnofsky Performance Scale (KPS) scores on the seventh-day post-surgery. Therefore, combining superficial temporal artery-middle cerebral artery bypass grafting surgery with a temporal muscle patch can result in better clinical outcomes for patients with Moyamoya disease, leading to a reduction in coma symptoms [62].

7.4. Combined Bypass

This surgical approach combines direct and indirect bypass techniques using the superficial temporal artery (STA) to the middle cerebral artery (MCA) anastomosis and encephaloduroarteriosynangiosis (EDAMS). The parietal branch is used for direct bypass, while the remaining STA branch is used for pial synangiosis. A study by Siang Lee *et al.* found that the rates of perioperative adverse events were similar between the direct/combined bypass (DB/CB) and indirect bypass (IB) groups, except for slightly higher wound complications in the DB/CB group. However, the rates of post-surgical revascularization favored DB/CB over IB. Therefore, combined bypass is a Reliable and efficient option for pediatric patients with moyamoya disease/moyamoya syndrome. However, there is insufficient evidence to conclusively support the notion that direct bypass or

collateral bypass may yield superior long-term angiographic revascularization results in comparison to indirect bypass [63].

7.5. Palliative Embolization Where Radiosurgery Is Not Suitable

Very rarely reported in recent studies, where surgical management is very challenging and even controversial, when there is incidental existence of Arteriovenous malformation with MMD (1.7 per 1000 persons), where the vascular circular to the affected area comes from the branches of the external carotid artery (ECA) that pass through the protective membrane surrounding the brain called the dura mater [64] [65]. The symptoms of neurodegenerative diseases, such as progressive focal deficits, seizures, cognitive decline, and other neurological symptoms, can make it difficult to recognize and diagnose these conditions [66]. De Leacy R *et al.* highlighted that treating arteriovenous malformation in patients who have non-hemorrhagic neurological deficits can be a difficult and debated task [67]. Interestingly, imperial embolization is the best for arteriovenous malformation and arteriovenous fistula patients. Nevertheless, still controversial exists, since there is no justifiable evidence that it is necessary to fully treat arteriovenous malformation (AVM) and arteriovenous fistula (AVF), as it is important to consider that the blood supply to the anterior cerebral artery (ACA) and middle cerebral artery (MCA) might be dependent on the AVM [68].

7.6. Future Promising Avenues: Role of Protein Connexin 43 on Moyamoya Disease

New and promising treatment options for Moyamoya disease have been discovered. A study by Liming Zhao *et al.* examined the effects of autologous bone marrow stem cell therapy (ABMSCT) on inflammatory factors and Conexin43 (Cx43) protein levels in patients with Moyamoya disease. The results showed that the experimental group had lower percentages of patients in higher disease grades (IV, III, and II) compared to the control group. Conversely, the experimental group had a higher percentage of patients in the lowest disease grade (I) compared to the control group. Additionally, the experimental group experienced reduced incidences of intracranial infection, hydrocephalus, hemiplegia, and transient neurological dysfunction [69]. These positive outcomes were attributed to the ABMSCT treatment's ability to decrease inflammatory response, remove damaged vascular tissues, and promote tissue repair, surpassing the benefits of surgical interventions.

8. Conclusion

The specific cause of Moyamoya disease (MMD) is still unknown, but research suggests that genetic factors and complex immune and inflammatory responses contribute to its development. While MMD can present with different clinical symptoms, surgical treatment remains the primary approach for achieving meaningful clinical improvements. The main challenge that remains is recognizing

Moyamoya disease as a potential diagnosis in all patients who exhibit signs of a stroke. It is crucial to promptly evaluate these patients and provide appropriate treatment options based on their specific conditions.

Availability of Data and Materials

The data used to support the findings in this review article are incorporated in the article.

Conflicts of Interest

The authors declare that they have no competing of interests regarding this article publication.

Authors' Contributions

The authors M. C. M conceived the idea; D. Y and M. C. M drafted and wrote the manuscript; D. Y and D. Z provided the cornerstone intellectual contents in writing up the manuscript. All authors have read and agreed to publish the article.

References

[1] Rupareliya, C. and Lui, F. (2023) Moyamoya Disease. StatPearls, Treasure Island, FL.

[2] Kondo, T. (2018) Moyamoya Disease. *CMAJ*, **190**, e1364. https://doi.org/10.1503/cmaj.180681

[3] Cardoso, I., Pinto, M., Araújo, A. and Vila-Real, M. (2023) Rare RNF213 Variant in Adolescent with Moyamoya Disease. *Review Neurology*, **76**, 177-181. https://doi.org/10.33588/rn.7605.2021392

[4] Ok, T., Jung, Y.H., Kim, J., Park, S.K., Park, G., Lee, S., *et al.* (2022) RNF213 R4810K Variant in Suspected Unilateral Moyamoya Disease Predicts Contralateral Progression. *Journal of American Heart Association*, **11**, e025676. https://doi.org/10.1161/JAHA.122.025676

[5] Mansuri, Z., Patel, K., Trivedi, C., Desai, S., Patel, S., Desai, R., *et al.* (2022) Burden of Psychiatric Disorders in Moyamoya Disease: A National Inpatient Perspective from 2007-2014. *Primary Care Companion for CNS Disorders*, **24**, 21m03157. https://doi.org/10.4088/PCC.21m03157

[6] Chen, Y., Tang, M., Li, H., Liu, H., Wang, J. and Huang, J. (2022) TGFβ1 as a Predictive Biomarker for Collateral Formation within Ischemic Moyamoya Disease. *Frontiers in Neurology*, **13**, Article 899470. https://doi.org/10.3389/fneur.2022.899470

[7] Okuyama, T., Kawabori, M., Ito, M., Sugiyama, T., Kazumata, K. and Fujimura, M. (2022) Outcomes of Combined Revascularization Surgery for Moyamoya Disease without Preoperative Cerebral Angiography. *World Neurosurgery*, **165**, e446-e451. https://doi.org/10.1016/j.wneu.2022.06.067

[8] Funaki, T., Takahashi, J.C., Houkin, K., Kuroda, S., Takeuchi, S., Fujimura, M., *et al.* (2018) Angiographic Features of Hemorrhagic Moyamoya Disease with High Recurrence Risk: A Supplementary Analysis of the Japan Adult Moyamoya Trial. *Journal of Neurosurgery*, **128**, 777-784. https://doi.org/10.3171/2016.11.JNS161650

[9] Zeng, C., Ge, P., Liu, C., Yu, X., Zhai, Y., Liu, W., *et al.* (2022) Association of Circulating Branched-Chain Amino Acids with Risk of Moyamoya Disease. *Frontiers in Nutrition*, **9**, Article 994286. https://doi.org/10.3389/fnut.2022.994286

[10] Montaner, J., Ramiro, L., Simats, A., Tiedt, S., Makris, K., Jickling, G.C., *et al.* (2020) Multilevel Omics for the Discovery of Biomarkers and Therapeutic Targets for Stroke. *Nature Reviews Neurology*, **16**, 247-264. https://doi.org/10.1038/s41582-020-0350-6

[11] Hao, X., Xu, L., Liu, Y., Luo, C., Yin, Y., Chen, X., *et al.* (2022) Construction of Diagnosis Model of Moyamoya Disease Based on Convolution Neural Network Algorithm. *Computational and Mathematical in Medicine*, **2022**, Article ID: 4007925. https://doi.org/10.1155/2022/4007925

[12] Mineharu, Y., Liu, W., Inoue, K., Matsuura, N., Inoue, S. and Takenaka, K. (2008) Autosomal Dominant Moyamoya Disease Maps to Chromosome 17q25.3. *Neurology*, **70**, 2357-2363. https://doi.org/10.1212/01.wnl.0000291012.49986.f9

[13] Kamada, K., Aoki, Y., Narisaw, A., Abe, Y., Komatsuzaki, S., Kikuchi, A., *et al.* (2011) A Genome-Wide Association Study Identifies RNF213 as the First Moyamoya Disease Gene. *Journal of Human Genetics*, **50**, 34-40. https://doi.org/10.1038/jhg.2010.132

[14] Miyawaki, S., Imai, H., Shimizu, M., *et al.* (2013) Genetic Variant RNF213 c.14576G>A in Various Phenotypes of Intracranial Major Artery Stenosis/Occlusion. *Stroke*, **44**, 2894-2897. https://doi.org/10.1161/STROKEAHA.113.002477

[15] Duan, L., Wei, L., Tian, Y., Zhang, Z., Hu, P., Wei, Q., *et al.* (2018) Novel Susceptibility Loci for Moyamoya Disease Revealed by a Genome-Wide Association Study. *Stroke*, **49**, 11-18. https://doi.org/10.1161/STROKEAHA.117.017430

[16] Hiraide, T., Suzuki, H., Momoi, M., Shinya, Y., Fukuda, K., Kosaki, K., *et al.* (2022) RNF213-Associated Vascular Disease: A Concept Unifying Various Vasculopathies. *Life* (*Basel*), **12**, Article 555. https://doi.org/10.3390/life12040555

[17] Pinard, A., Fiander, M.D.J., Cecchi, A.C., Rideout, A.L., Azouz, M., *et al.* (2021) Association of *De Novo* RNF213 Variants with Childhood Onset Moyamoya Disease and Diffuse Occlusive Vasculopathy. *Neurology*, **96**, e1783-e1791. https://doi.org/10.1212/WNL.0000000000011653

[18] Uchino, H., Kuroda, S., Hirata, K., Shiga, T. and Houkin, K. (2012) Autoimmune-Mediated Inflammation in Moyamoya Disease: A Review. *Neurologia Medico-Chirurgica* (*Tokyo*), **52**, 837-844.

[19] Herve, D., Chretien, F., Benouaich-Amiel, A., *et al.* (2003) A Hereditary Moyamoya Syndrome with Multisystemic Manifestations. *Neurology*, **61**, 1821-1824.

[20] Louvrier, C., Awad, F., Cosnes, A., El Khouri, E., Assrawi, E., Daskalopoulou, A., *et al.* (2022) RNF213-Associated Urticarial Lesions with Hypercytokinemia. *Journal of Allergy and Clinical Immunology*, **150**, 1545-1555. https://doi.org/10.1016/j.jaci.2022.06.016

[21] Scott, R.M. and Smith, E.R. (2009) Moyamoya Disease and Moyamoya Syndrome. *The New England Journal of Medicine*, **360**, 1226-1237. https://doi.org/10.1056/NEJMra0804622

[22] Inaba, M., Henmi, Y., Kumeda, Y., Ueda, M., Nagata, M., Emoto, M., *et al.* (2002) Increased Stiffness in Common Carotid Artery in Hyperthyroid Graves' Disease Patients. *Biomedicine & Pharmacotherapy*, **56**, 241-246. https://doi.org/10.1016/S0753-3322(02)00195-6

[23] Pinardi, F., Stracciari, A., Spinardi, L. and Guarino, M. (2013) Postpneumococcal Moyamoya Syndrome Case Report and Review of the Postinfective Cases. *BMJ Case*

Reports, **2013**, bcr2012006726. https://doi.org/10.1136/bcr-2012-006726

[24] Braun, K.P.J., Bulder, M.M.M., Chabrier, S., Kirkham, F.J., Uiterwaal, C.S.P., Tardieu, M., *et al.* (2009) The Course and Outcome of Unilateral Intracranial Arteriopathy in 79 Children with Ischaemic Stroke. *Brain*, **132**, 544-557. https://doi.org/10.1093/brain/awn313

[25] Ueno, M., *et al.* (2002) Unilateral Occlusion of the Middle Cerebral Artery after Varicella-Zoster Virus Infection. *Brain and Development*, **24**, 106-108. https://doi.org/10.1016/S0387-7604(02)00005-0

[26] Ghosh, R., *et al.* (2020) COVID-19 Presenting with Thalamic Hemorrhage Unmasking Moyamoya Angiopathy. *Canadian Journal of Neurological Sciences*, **47**, 849-851. https://doi.org/10.1017/cjn.2020.117

[27] Han, H., Pyo, C.W., Yoo, D.S., *et al.* (2016) Detection of Human Herpesvirus 6 Variant A in Peripheral Blood Mononuclear Cells from Patients with Idiopathic Moyamoya Disease. *Journal of Clinical Microbiology*, **54**, 2021-2024.

[28] Kikuta, K.I., Takagi, Y., Nozaki, K., *et al.* (2008) Expression of Interferon-Induced Genes after Viral Infection in Patients with Idiopathic Moyamoya Disease. *Surgical Neurology*, **69**, 233-238.

[29] Das, S., *et al.* (2021) Impact of COVID-19 Pandemic in Natural Course of Moyamoya Angiopathy: An Experience from Tertiary-Care-Center in India. *Egyptian Journal of Neurology, Psychiatry and Neurosurgery*, **57**, Article No. 166. https://doi.org/10.1186/s41983-021-00412-2

[30] Wallace, S., *et al.* (2016) Disrupted Nitric Oxide Signaling Due to GUCY1A3 Mutations Increases Risk for Moyamoya Disease, Achalasia and Hypertension. *Clinical Genetics*, **90**, 351-360. https://doi.org/10.1111/cge.12739

[31] Guo, D.C., *et al.* (2009) Mutations in Smooth Muscle Alpha-Actin (ACTA2) Cause Coronary Artery Disease, Stroke, and Moyamoya Disease, Along with Thoracic Aortic Disease. *The American Journal of Human Genetics*, **84**, 617-627. https://doi.org/10.1016/j.ajhg.2009.04.007

[32] Xin, B., *et al.* (2011) Homozygous Mutation in SAMHD1 Gene Causes Cerebral Vasculopathy and Early Onset Stroke. *Proceedings of the National Academy of Sciences of the United States of America*, **108**, 5372-5377. https://doi.org/10.1073/pnas.1014265108

[33] Miskinyte, S., *et al.* (2011) Loss of BRCC3 Deubiquitinating Enzyme Leads to Abnormal Angiogenesis and Is Associated with Syndromic Moyamoya. *The American Journal of Human Genetics*, **88**, 718-728. https://doi.org/10.1016/j.ajhg.2011.04.017

[34] Guey, S., *et al.* (2017) *De Novo* Mutations in CBL Causing Early-Onset Paediatric Moyamoya Angiopathy. *Journal of Medical Genetics*, **54**, 550-557. https://doi.org/10.1136/jmedgenet-2016-104432

[35] Li, J., Ge, P., He, Q., Liu, C., Zeng, C., Tao, C., *et al.* (2023) Association between Methionine Sulfoxide and Risk of Moyamoya Disease. *Frontiers in Neuroscience*, **17**, Article 1158111. https://doi.org/10.3389/fnins.2023.1158111

[36] Su, Y., Li, G., Zhao, H., Feng, S., Lu, Y., Liu, J., Chen, C., *et al.* (2022) the Relationship between Hemoglobin and Triglycerides in Moyamoya Disease: A Cross-Sectional Study. *Frontiers in Neurology*, **13**, Article 994341. https://doi.org/10.3389/fneur.2022.994341

[37] Li, S., Han, Y., Zhang, Q., Tang, D., Li, J. and Weng, L. (2022) Comprehensive Molecular Analyses of An Autoimmune-Related Gene Predictive Model and Immune Infiltrations Using Machine Learning Methods in Moyamoya Disease. *Frontiers in Molecular Biosciences*, **9**, Article 991425.

https://doi.org/10.3389/fmolb.2022.991425

[38] Guevara-Rodriguez, N., Marmanillo-Mendoza, G., Castelar, J., Ciobanu, C. and Fulger, I. (2023) Unusual Presentation of Acquired Thrombotic Thrombocytopenic Purpura (TTP) versus Catastrophic Antiphospholipid Syndrome in a Patient with Moya-Moya Disease, Case Report, and Literature Review. *Clinical Case Reports*, **11**, e7317. https://doi.org/10.1002/ccr3.7317

[39] Kuroda, S. and Houkin, K. (2008) Moyamoya Disease: Current Concepts and Future Perspectives. *The Lancet Neurology*, **7**, 1056-1066. https://doi.org/10.1016/S1474-4422(08)70240-0

[40] Suzuki, J. and Kodama, N. (1983) Moyamoya Disease—A Review. *Stroke*, **14**, 104-109. https://doi.org/10.1161/01.STR.14.1.104

[41] White, T., Gandhi, S., Langer, D.J., Katz, J.M. and Dehdashti, A.R. (2022) Does Advanced Imaging Aid in the Preoperative Evaluation of Patients with Moyamoya Disease? *Cureus*, **14**, e29816. https://doi.org/10.7759/cureus.29816

[42] Hishikawa, T., Sugiu, K. and Date, I. (2016) Moyamoya Disease: A Review of Clinical Research. *Acta Medica Okayama*, **70**, 229-236.

[43] Zhao, M.Y., Fan, A.P., Chen, D.Y.-T., Ishii, Y., Khalighi, M.M., Moseley, M., *et al.* (2022) Using Arterial Spin Labeling to Measure Cerebrovascular Reactivity in Moyamoya Disease: Insights from Simultaneous PET/MRI. *Journal of Cerebral Blood Flow Metabolism*, **42**, 1493-1506. https://doi.org/10.1177/0271678X221083471

[44] Hara, S., Tanaka, Y., Ueda, Y., Hayashi, S., Inaji, M., Ishiwata, K., *et al.* (2017) Noninvasive Evaluation of CBF and Perfusion Delay of Moyamoya Disease Using Arterial Spin-Labeling MRI with Multiple Postlabeling Delays: Comparison with 15O-Gas PET and DSC-MRI. *American Journal of Neuroradiology*, **38**, 696-702. https://doi.org/10.3174/ajnr.A5068

[45] Li, J., Zhang, Y., Yin, D., Shang, H., Li, K., Jiao, T., *et al.* (2022) CT Perfusion-Based Delta-Radiomics Models to Identify Collateral Vessel Formation after Revascularization in Patients with Moyamoya Disease. *Frontiers in Neuroscience*, **16**, Article 974096. https://doi.org/10.3389/fnins.2022.974096

[46] Zhang, H., Lu, M., Liu, S., Liu, D., Shen, X., Sheng, F., *et al.* (2022) The Value of 3D Pseudo-Continuousarterial Spin Labeling Perfusion Imaging in Moyamoya Disease—Comparison with Dynamic Susceptibility Contrast Perfusion Imaging. *Frontiers in Neurosciences*, **16**, Article 944246. https://doi.org/10.3389/fnins.2022.944246

[47] Chen, J., Yang, W., Zhang, H., *et al.* (2018) Transcranial Doppler Ultrasonography for Moyamoya Disease Before and after Revascularization Surgery: A Systematic Review and Meta-Analysis. *Journal of Ultrasound in Medicine*, **37**, 2759-2768.

[48] Kim, S.K., Wang, K.C., Kim, I.O., *et al.* (2009) Moyamoya Disease: Treatment and Outcomes. *Journal of Korean Neurosurgical Society*, **46**, 525-531.

[49] Larson, A.S., Klaas, J.P., Johnson, M.P., Benson, J.C., Shlapak, D., Lanzino, G., *et al.* (2022) Vessel Wall Imaging Features of Moyamoya Disease in a North American Population: Patterns of Negative Remodelling, Contrast Enhancement, Wall Thickening, and Stenosis. *BMC Medical Imaging*, **22**, Article No. 198. https://doi.org/10.1186/s12880-022-00930-2

[50] Lu, J., Xia, Q., Yang, T., Qiang, J., Liu, X., Ye, X., *et al.* (2020) Electroencephalographic Features in Pediatric Patients with Moyamoya Disease in China. *Chinese Neurosurgical Journal*, **6**, Article No. 3. https://doi.org/10.1186/s41016-019-0179-2

[51] Zhang, Z., Wang, Y., Zhou, S., Li, Z., Peng, Y., Gao, S., *et al.* (2023) The Automatic

Evaluation of Steno-Occlusive Changes in Time-of-Flight Magnetic Resonance Angiography of Moyamoya Patients Using a 3D Coordinate Attention Residual Network. *Quantitative Imaging in Medicine and Surgery*, **13**, 1009-1022. https://doi.org/10.21037/qims-22-799

[52] Hishikawa, T., Sugiu, K. and Date, I. (2016) Moyamoya Disease: A Review of Clinical Research. *Acta Medica Okayama*, **70**, 229-236.

[53] Porras, J.L., Yang, W., Xu, R., Garzon-Muvdi, T., Caplan, J.M., Colby, G.P., *et al.* (2018) Effectiveness of Ipsilateral Stroke Prevention between Conservative Management and Indirect Revascularization for Moyamoya Disease in a North American Cohort. *World Neurosurgery*, **110**, e928-e936. https://doi.org/10.1016/j.wneu.2017.11.113

[54] Hamada, Y., Shigehisa, A., Kanda, Y., Ikeda, M., Takaguchi, G., Matsuoka, H., *et al.* (2023) Enhancement of the Ivy Sign during an Ischemic Event in Moyamoya Disease. *The Japanese Society of Internal Medicine*, **62**, 617-621. https://doi.org/10.2169/internalmedicine.9326-22

[55] Kim, J.Y., Kim, H.J., Choi, E.-H., Pan, K.H., Chung, J.-W., Seo, W.-K., *et al.* (2022) Vessel Wall Changes on Serial High-Resolution MRI and the Use of Cilostazol in Patients with Adult-Onset Moyamoya Disease. *Journal of Clinical Neurology*, **18**, 610-618. https://doi.org/10.3988/jcn.2022.18.6.610

[56] Ge, P.C., Ye, X., Zhang, Q., Zhang, D., Wang, S. and Zhao, J.Z. (2018) Encephaloduroateriosynangiosis versus Conservative Treatment for Patients with Moyamoya Disease at Late Suzuki Stage. *Journal of Clinical Neuroscience*, **50**, 277-280. https://doi.org/10.1016/j.jocn.2017.12.004

[57] Nguyen, V.N., Parikh, K.A., Motiwala, M., Miller, L.E., Barats, M., Milton, C., *et al.* (2022) Surgical Techniques and Indications for Treatment of Adult Moyamoya Disease. *Frontiers in Surgery*, **9**, Article 966430. https://doi.org/10.3389/fsurg.2022.966430

[58] Fiaschi, P., Scala, M., Piatelli, G., Tortora, D., Secci, F., Cama, A., *et al.* (2021) Limits and Pitfalls of Indirect Revascularization in Moyamoya Disease and Syndrome. *Neurosurgical Review*, **44**, 1877-1887. https://doi.org/10.1007/s10143-020-01393-1

[59] Wang, Y., Li, M. and Wang, J. (2022) Indirect Revascularization vs. Non-Surgical Treatment for Moyamoya Disease and Moyamoya Syndrome: A Comparative Effectiveness Study. *Frontiers in Neurology*, **13**, Article 1041886. https://doi.org/10.3389/fneur.2022.1041886

[60] Sreenivasan, S.A., Suri, A., Raheja, A., Phuyal, S., Singh, M., Mishra, S., *et al.* (2022) Effect of Age, Stage, and Type of Surgical Revascularization on Clinical and Angiographic Outcome in Moyamoya Disease—Experience from a Case Series of 175 Revascularization Procedures. *Journal of Neurological Society of India*, **70**, 2072-2081. https://doi.org/10.4103/0028-3886.359200

[61] Bao, X.-Y. and Duan, L. (2023) Chinese Expert Consensus on the Treatment of MMD. *Chinese Neurosurgical Journal*, **9**, Article No. 5. https://doi.org/10.1186/s41016-023-00318-3

[62] Gao, F., Chen, S., Gu, J., Wang, Z. and Wang, Z. (2023) Clinical Efficacy of Superficial Temporal Artery-Middle Cerebral Artery Bypass Grafting Surgery Combined with Temporal Muscle Patch on Patients with Moyamoya Disease. *Journal of Craniofacial Surgery*, **34**, 643-649. https://doi.org/10.1097/SCS.0000000000008992

[63] Lee, K.S., Zhang, J.J.Y., Bhate, S., Ganesan, V., Thompson, D., James, G., *et al.* (2023) Surgical Revascularizations for Pediatric Moyamoya: A Systematic Review, Meta-Analysis, and Meta-Regression Analysis. *Child's Nervous System*, **39**, 1225-1243. https://doi.org/10.1007/s00381-023-05868-6

[64] Nurimanov, C., Mammadinova, I., Makhambetov, Y. and Akshulakov, S. (2023) An Uncommon Case of Moyamoya Syndrome Is Accompanied by an Arteriovenous Malformation with the Involvement of Dural Arteries. *International Journal of Molecular Sciences*, **24**, Article 5911. https://doi.org/10.3390/ijms24065911

[65] Feria, A. and Brzezicki, G. (2021) Ruptured Temporal Horn Aneurysm Associated with Moyamoya Collateral Vessel Coexisting with Contralateral Arteriovenous Malformation—Technical Note with Clinical Vignette. *Neurologia i Neurochirurgia Polska*, **55**, 102-106. https://doi.org/10.5603/PJNNS.a2021.0004

[66] Park, H., Lee, E.J., Cheon, J.-E., Kim, J.E., Kang, H.-S. and Kim, S.-K. (2021) Clinical Features and Treatment Outcomes of Cerebral Arteriovenous Malformation Associated with Moyamoya Disease. *World Neurosurgery*, **154**, e633-e640. https://doi.org/10.1016/j.wneu.2021.07.100

[67] De Leacy, R., Ansari, S.A., Schirmer, C.M., Cooke, D.L., Prestigiacomo, C.J., Bulsara, K.R., *et al.*, SNIS Standards and Guidelines Committee (2022) SNIS Board of Directors Endovascular Treatment in the Multimodality Management of Brain Arteriovenous Malformations: Report of the Society of NeuroInterventional Surgery Standards and Guidelines Committee. *Journal of NeuroInterventional Surgery*, **14**, 1118-1124. https://doi.org/10.1136/neurintsurg-2021-018632

[68] Hou, K., Zhao, Y., Chen, X., Xu, K. and Yu, J. (2020) Moyamoya Disease Concurrent with Dural Arteriovenous Fistula: A Case Report and Literature Review. *Experimental and Therapeutic Medicine*, **20**, Article No. 161. https://doi.org/10.3892/etm.2020.9290

[69] Zhao, L., Li, T., Xue, B., Liang, H., Zhang, S., Wu, R., *et al.* (2022) Influence of Autologous Bone Marrow Stem Cell Therapy on the Levels of Inflammatory Factors and Conexin43 of Patients with Moyamoya Disease. *Computational Intelligence and Neuroscience*, **2022**, Article ID: 7620287. https://doi.org/10.1155/2022/7620287