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Moyamoya Disease: An Overview

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ABSTRACT

Moyamoya Disease (MMD) is an idiopathic progressive cerebrovascular disease (CVD) affecting the population irrespective of age that was reported for the first time in 1960s in Japan. MMD is an uncommon genetic disorder with considerable morbidity and mortality rate with increased incidence in Eastern Asia. Ring Finger Protein 213(RNF213) is a susceptibility gene for MMD. Studies suggest that abnormalities in angiogenesis and vasculogenesis prove to be the potential disease mechanisms. Cerebral ischemia and intracranial haemorrhage are the most commonly observed symptoms of MMD. The disease is incurable but manageable with medical therapy consisting of anticoagulants, antiepileptics and surgical revascularisation. Identifying the limitations of the existing research is essential for advancing progress in this field. This scientific statement outlines novel prospects for future research initiatives.

INTRODUCTION

Moyamoya disease (MMD) is an uncommon progressive vaso-occlusive disorder characterised by an unclear aetiology. It occurs by gradual stenosis of terminal part of internal carotid arteries bilaterally, the circle of Willis and the main trunks of anterior and middle cerebral artery and is linked with formation of collateral vessels at the base of the brain [1].

In 1969, Suzuki and Takaku were the first to publish the term “Moyamoya disease” in an English journal. In the 1970s, the Japanese Ministry of Health and Welfare organized the Research Committee on Moyamoya Disease (RCMD) to give integrated diagnosis, treatment, and preventive measures. This research group first established the guidelines for diagnosis of MMD in 1978, and has revised them since then on 5 occasions [2].

The disease can be described with complicated clinical manifestations. The origin of the disease was first reported in 1950s. The studies of genomics and pathophysiology of Moyamoya disease have also promoted the scope of trying to understand it’s unclear aetiology[3].Numerous studies conducted across the globe have attempted better understanding of the epidemiological aspects of the disease in different areas. With the advancement and application of techniques in the field of radiology, numerous neuro imaging methods with different benefits have promoted the cognizance of MMD related to its structure and function along with its temporal and spatial aspects [4].

As of now, the predominant elements of treatment for MMD include neurological safety, cerebral blood flow reconstruction, neurological rehabilitation, drug therapy, surgical revascularization, and cognitive rehabilitation. In this review, we explore the current improvements in the nature of clinical features, neuro imaging evaluation and treatment of MMD, to accentuate future prospectives in the field of medicine [5].

GENETICS

Up to 12% of Patients with MMD have a positive family history, indicating a significant genetic linkage. Findings related to genetic mutations involved in the pathogenesis of MMD is vital to comprehending the pathophysiology of the disease and locating inherent therapeutic targets [6]. The Ring Finger Protein 213 (RNF213) is a susceptibility gene for MMD, and RNF213 p.R4810K is a major variant for East Asians, specifically in Japanese and Korean, on the other hand non R4810K variants accelerate the risk of MMD in non–East Asian and defined Chinese populations [7].

Several genes have been identified to play a role, at least partially, in the pathogenesis of the vasculopathy. RNF213 plays a role in cerebrovascular angiogenesis and remodelling. RNF213 physiologically functions as a E3 ubiquitin ligase. Henceforth, defective or hypo morphic RNF213 p.R4810K function may be unsuccessful in degrading the 2 substrates, NFAT1 and filamin A.

Most of the RNF213 mutations are predominantly missense mutations and are identified at the C terminals. This advocates that the mutations have an ascendant negative or gain-of-function effect. Most of the RNF213 mutations do not fall into the classification of null mutations, resulting in a loss-of-function (nonsense or frame-shift mutations) [8]. Recent molecular studies have indicated that RNF213 may play a role as an antimicrobial protein with crucial functions in the immune system.

Finally, there are other genes that have been hinted in the development of MMD, like mutations in the genes ACTA2 and GUCY1A3 in rare situations [9].

EPIDEMIOLOGY

There are significant geographical variations in the incidence of MMD, with a high prevalence in East Asia and a low prevalence in other regions. With respect to previous studies, the prevalence of MMD is 10.5/100,000 individuals and the incidence rate is 0.94/100,000 individuals in Japan [10]. The prevalence rate is 16.1/100,000 and the incidence rate is 2.3/100,000 individuals in South Korea. The incidence of MMD was as low as 0.09/100,000 individuals in other places, including North America, but it has showed an ascending trend in the US (17the prevalence of MMD in the time frame of 2000-2007 was 3.92/100,000) in Nanjing (China) [11].

According to the latest study, since 1976, 2,430 cases of MMD have been reported in China. Globally, the age of onset of MMD is considerably bimodal in distribution, with a bimodal peak consisting of a major peak in the first decade of life and a moderate peak in the late 20 to 30s[12].Consequentially, geographic differences in sex distribution have also been spotted. The incidence of MMD in females was reported to be higher than that in males with the male-to-female ratio ranging from 1:1.8 to 1:2.2 in foreign populations. Having said that, the sex ratio is 1:1 in China [13].

PATHOPHYSIOLOGY

A number of hypotheses have been stated, such as inflammation, abnormal endothelial progenitor cells (EPCs), and stimulation of angiogenic factors. Since altered amounts of cytokines, chemokines, and growth factors were found in the serum and cerebrospinal fluid (CSF) of MMD patients. Earlier studies postulated that abnormalities in angiogenesis and vasculogenesis prove to be potential disease causes. Following that, the association between MMD and numerous hereditary conditions (including Down syndrome, sickle cell disease, and neurofibromatosis type 1), the high familial rate, and the strong link between this disease and variants of the Ring Finger Protein 213 (RNF213) gene in patients in East Asia confirmed the involvement of genetic factors in the pathogenesis of MMD. As a result, the focus of research has been drastically altered and the researchers focusing on the biological impact of mutant RNF213 is now larger.

However, it's probable that all of these pathways contribute to the pathophysiology of the disease. MMA results from a complex mechanism in which acquired infectious, inflammatory and flow-dynamic conditions might trigger the disease in genetically susceptible individuals through abnormalities in angiogenic and vasculogenic pathways. Moreover, the emergence of microaneurysms has been hypothesized as an additional pathophysiologic explanation; small aneurysms arising from collateral vessels have been linked with intraventricular haemorrhage. Due to the lack of specific in-vivo and in-vitro disease experimental models comprehending MMA is demanding and restricted. To enhance our understanding of disease causes, a number of preclinical in vivo or in vitro MMA models, including as EPCs, smooth muscle cells (SMCs), iPSC, RNF213-KO animal models, or latest surgical models, are set up. It has been explained that endovascular thrombosis and hyperplasia of smooth muscle cell contribute to the pathophysiology of ischemic cerebrovascular events by causing increasing stenosis or blockage of the distal ICA. Histopathological findings in the carotid terminations include fibro cellular thickening of the intima, irregular waving of the internal elastic lamina, and attenuation of the media, all paving way to the progressive luminal stenosisin the carotid fork. However, it has also been shown that, in contrast to atherosclerotic degradation, the outer diameter decreases simultaneously.

In addition to that, increasing evidence bolsters the hypothesis that artery-to-artery embolism may also result in ischemic events based on microemboli signal (MES) monitoring by

transcranial ultrasound, largely in the early phase of the disease and after recently seen ischemic stroke [14].

CLINICAL PRESENTATION

The onset of MMD may develop MMD at any age, from childhood to adulthood. The most frequent symptoms are intracranial haemorrhage and cerebral ischemia. The early manifestations include headache, seizures, movement disorders, haemorrhage, transient ischemic attack (TIA), ischemic stroke, and cognitive impairment. Despite being the most common presentations, ischemic and haemorrhagic episodes have different frequency in paediatric and adult patients. In children and adolescents, ischemia is the most frequent manifestation (73.9–97.5% of cases); haemorrhage is far less prevalent (occurring in just 2.5–8.0%). Adults with MMD have a greater incidence of intracranial haemorrhage (19.1-42.3%) but a lower incidence of transient ischemic attack (TIA) or cerebral infarction (57.7–70.0%).

Changes in age, territory of vascular involvement, stenosis severity, and brain territories affected are the factors for a wide range of clinical manifestations and timeframes. Conventionally, the advancement of arterial stenosis results in cerebral hypoperfusion, causing multiple and recurrent ischemic events [14]. TIA is more common in children and adolescents whereas cerebral infarction is more common in adults. TIA episodes frequently occur during hyper ventilation in paediatric patients with MMD due to crying or are caused by fever or dehydration. These triggers may induce vasoconstriction or an overall reduction in cerebral blood flow (CBF), which is characterised by the fact that cerebral metabolic demand is much higher in the first decade of life, decreasing thereafter [15]. Lacunar infarcts show greater functional results following revascularization, and the probability of symptomatic MMD recurrence is 18% in the first year following the initial presentation and rises by 5% each year thereafter, with a 5-year cumulative risk of almost 40%. However, the clinical course and results may deteriorate due to ischemia events that affect the posterior circulation, which includes the regions of the vertebral artery, basilar artery, and posterior cerebral artery (PCA). In people with MMD, the white matter is more vulnerable to damage than the grey matter, and such damage can lead to cognitive impairment. Cerebral haemorrhage is more common in adults with MMD, and often has poorer results than in children and adolescents [14].

Cerebral haemorrhage occurs as a result of friable collateral rupture often in intra ventricular and lobar areas, since majority of the collateral vessels originate from the choroidal system

that has been inked with aneurysms. A further potential source of bleeding is the posterior communicating arteries, and the presence of multiple microbleeds is an indicative of the development of more clinically significant haemorrhage in the future. Unstable MMD characterized as cases of rapid progression or recurrent stroke, is a more clinically challenging condition that is primarily observed in children under three years of age and in those with underlying disorders. Unstable MMD is a potential risk factor for perioperative ischemic complications, and thus identifying it early can improve surgical outcomes by creating a window of opportunity for perioperative-focused care and surgical risk assessment. Around 3–4% of children with MMD manifest, movement disorders, occurring even less frequently among adults; the most common forms are hemichorea-hemiballismus or chorea-ballismus, followed by dystonia (segmental, generalized, hemidystonia, or acute status dystonicus) and less frequently, ataxia, myoclonus, and isolated limb shaking [16]. Any of those may occur in combination, and each may manifest as a continuous, paroxysmal, or hyper ventilation-induced phenomenon [17].

DIAGNOSIS

When patients, particularly children, present with acute neurologic impairments or unexplained symptoms suggestive of cerebral ischemia, Moyamoya should be taken into consideration and diagnostic examination should be initiated. Delays in diagnosis lead to delays in treatment, which increases the likelihood of permanent impairment from stroke. Referring patients with Moyamoya or suspected Moyamoya to hospitals skilled in treating such cases is extremely crucial.

Any patient who exhibits unexplained symptoms suggestive of cerebral ischemia should be suspected of developing Moyamoya. Radiographic investigations readily confirm the existence of Moyamoya, despite the wide differential diagnosis for these symptoms. When a patient is suspected of having Moyamoya, several investigations are often required for radiographic assessment [18].

Computed tomography (CT)

In a patient with moyamoya disease, their CT scan can exhibit small, hypodensity areas in the cortical watershed zones, basal ganglia, deep white matter, or periventricular areas that might indicate a stroke or haemorrhage. Even yet, the CT scan may still be normal, especially in patients who are just exhibiting TIAs. The intracranial stenoses seen in moyamoya can be

seen on CT angiography. Consequently, when cerebral occlusive vasculopathy is being investigated as a diagnosis and magnetic resonance imaging (MRI) is not easily accessible, CT angiography should be taken into consideration [19].

Magnetic resonance imaging (MRI)

Due to widespread availability, magnetic resonance angiography and MRI are now often used as main imaging techniques in patients exhibiting symptoms indicative with Moyamoya. Diffusion-weighted imaging has a greater probability of identifying an acute infarct, whereas T1- and T2-weighted imaging is more likely to indicate a chronic infarct. Decline in cortical blood flow due to Moyamoya can be concluded from fluid-attenuated inversion recovery (FLAIR) sequences showing linear high signals that follow a sulcal pattern, which is called the “ivy sign”. Reduced flow voids in the internal, middle, and anterior cerebral arteries in addition to significant flow voids originating from, Moyamoya-associated collateral vessels via the basal ganglia and thalamus constitute the MRI findings that are most typical of Moyamoya. These findings are virtually diagnostic of Moyamoya [18].

Angiography

A complete five- or six-vessel examination including the external and internal carotid arteries as well as one or both vertebral arteries should be included in the angiography, depending on the collateral patterns observed. Patients with MMD did not have higher complication rates than patients with any other kind of cerebrovascular illness, according to a research done on 190 patients having diagnostic angiography. The final diagnosis is predicated on a distinct arteriographic appearance that includes proximal anterior and middle artery stenosis as well as distal intracranial internal carotid artery stenosis. Severity of the disease is often categorised into one of six progressive stages that were at first defined in 1969[20].In the intermediate stages of the Suzuki grading system quoted in Table 1, there is a notable development of a large collateral network at the base of the brain along with the distinctive "puff of smoke" appears on angiography. It is essential to do external carotid artery imaging to identify any collateral vessels that may already be present so that any future surgery won't damage them. Conventional angiography is the most effective method for identifying aneurysms and the uncommon arteriovenous malformation that has been related to certain cases of Moyamoya patients. Further diagnostic assessments that might be useful in assessing patients with Moyamoya include cerebral blood-flow investigations and

electroencephalography (EEG). Specific alterations of EEG recordings, which are usually noted only in children [18].

Table 1 - Suzuki Grading system [32]

Stage 1	Narrowing of carotid fork
Stage 2	Initiation of the moyamoya and dilatation of intracranial main arteries
Stage 3	Intensification of the moyamoya and defects of the ACA and MCA
Stage 4	Minimization of the moyamoya and defects of the PCA
Stage 5	Reduction of the moyamoya and development of ECA collaterals
Stage 6	Disappearance of the moyamoya and circulation only via ECA and VA

[ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; ECA, external carotid artery; VA, vertebral artery]

TREATMENT

Medical treatment in terms of treating the usual symptoms of MMD, the use of antiplatelet and many other agents focuses on symptomatic control. The results of a nationwide survey in Japan displayed that the selection of antiplatelet drugs treatment. Particularly, some researches showcased that cilostazol enhances cerebral perfusion as well as cognition better than other antiplatelet drugs for ischemic MMD patients. Whereas, a recent 10-year follow-up evaluation has exhibited that the use of antiplatelet agents did not influence the rate of cerebral infarction in patients with MMD [21]. In the AMORE trial, indications of treatment for patients with MMD who are asymptomatic are presently being revisited. A lot of research evidences is needed to affirm the efficiency of conservative therapy with antiplatelet drugs. Given the vascular cognitive impairment caused by MMD, acetylcholinesterase inhibitors, such as donepezil and rivastigmine, have usually been approved for modest cognitive benefits [22]. Besides, butylphthalide may attenuate perioperative neurological deficits in cases with unfavourable preoperative status. When administered together, efficacy of medical treatment for MMD remains unsure and more investigations are essentially required [13]. A large survey from Japan showed no significant differences in outcome between medically and surgically treated patients with Moyamoya, although a more recent review revealed that 38% of 651

patients with Moyamoya who were initially treated medically ultimately underwent surgery because of progressive symptoms [23].

Antiplatelet therapies have been used to prevent emboli from microthrombi that are formed at arterial stenosis sites, which can induce ischemic symptoms in patients with Moyamoya. Although these agents aren't used worldwide, they are now often given to patients in several surgical series. Low molecular weight heparin has been used with significant efficacy, whereas anticoagulants like warfarin are rarely administered [24]. Calcium-channel blockers may help to reduce the severity and frequency of refractory Transient Ischemic Attacks (TIAs), which are typically experienced by people with Moyamoya. They also assist in reducing uncontrollably occurring headaches or migraines which is commonly observed in patients with MMD. Since calcium-channel blockers may cause hypotension, they must be used with caution in this patient population [18]. Pharmacological treatment is directed at aggressive prevention of new neurovascular events and no single-drug regimen is accepted as a gold standard for ischemic or haemorrhagic complications [17].

SURGICAL INTERVENTION

Clinical evidence has shown the preventive benefit of surgical revascularization therapy on the incidence of ischemic stroke in individuals with ischemic MMD. Nonetheless, there is controversy on the use of intra- and extracranial revascularization in patients with hemorrhagic MMD to prevent bleeding from reoccurring. Duan et al conducted a review in patients with MMD and concluded that the possibility of recurrence of cerebral ischemia or cerebral haemorrhage in patients subjected to surgical re-vascularization was considerably lower in comparison with the patients who received conservative treatment[25]. Research conducted in 2010on Japanese adult population with MMD defined the primary and secondary end points as all as adverse events and rebleeding attacks, respectively. It was reported that for patients with haemorrhagic MMD, the difference between the surgical and non-surgical group was statistically significant, and a Kaplan-Meier analysis suggested that the collateral circulation given by the surgery was capable of preventing recurrent bleeding [26].

Consequently, the general consensus is that surgical intervention is necessary for patients with ischemic or haemorrhagic MMD. Surgical revascularization of MMD consists of 3 types: Direct revascularization, indirect revascularization and combined revascularization. The preferred approach in direct revascularization surgery is the superficial

temporal artery–Middle Cerebral Artery (MCA) anastomosis. The superficial temporal artery-Carotid Anterior cerebral Artery (ACA) or occipital artery-posterior cerebral artery anastomosis may be adopted when ischemic hypoperfusion happens in the blood supplying area of the ACA or posterior cerebral artery.[27]. Indirect revascularization is a surgery based on a variety of tissues used as a source of blood supply, mainly including Encephalomyosynangiosis, Encephaloduroarteriosynangiosis, multiple burr hole surgery, Encephaloduromyoarteriosynangiosis, encephalo-duro-myo-arterio-pericranial synangiosis and omental transplantation [28]. The combination of the former two revascularization techniques is called combined revascularisation. A recent meta-analysis discloses that direct or combined revascularization surgery is preferable for unstable adult patients with MMD who exhibit hemodynamic instability or symptoms.

It is crucial to actively prevent ischemia problems during the peri-operative phase, particularly in paediatric MMD patients. Transient neurological impairment resulting from altered hemodynamic is a common observation in majority of patients undergoing direct vascular bypass surgery. Competition between the blood flow from the superficial temporal artery bridge blood vessels and the blood flow from the existing collateral circulation leads to damage to the cerebrovascular auto-regulation function ending in the hypoperfusion of brain tissues and therefore, changes in hemodynamicis primarily observed [29]. Studies have displayed that ~1/4 of patients with direct bypass may agonize from high perfusion symptoms, and there was an increased risk of high perfusion in adult patients with MMD and patients with haemorrhagic MMD [30].A study carried out using positron emission tomography (PET) revealed that while cerebral blood flow and cerebral blood volume (CBV) increases, the oxygen extraction fraction (OEF) declined under high perfusion. The surge in pre-operative CBV or OEF is a risk factor for post-operative high perfusion when talking in terms of hemodynamic [31]. It is vital to closely monitor the fluctuations in the blood pressure in patients at the time of peri-operative period, to ward off the eventuality of low or excessive perfusion [13].

CONCLUSION

There are still many unanswered questions about our understanding of MMD. Even though the terminology used for their designation has improved, there are still a number of limitations. For example, it is still necessary to develop unified diagnostic criteria, identify

and validate specific markers, pinpoint the exact pathophysiological processes involved, and generate convincing data to provide treatment protocols and guidelines.

Recognizing the drawbacks and impediments of the published research is crucial to develop a novel strategy for overcoming such hurdles. The quality of studies available in Moyamoya is hindered by common factors such as limited disease process replication models in basic and translational research lack of globally accepted terminology and diagnostic criteria , limited sample sizes in published therapeutic research, and the unintentional introduction of selection bias in available therapeutic comparative studies due to methodological decisions about patient assignment to treatment groups based on the quality of the vessels to act as donors or clinical baseline condition.

There is a fundamental necessity to verify suitable surrogate indicators that have therapeutic significance. Future advancements in the methodology of Moyamoya research should take into account the application of innovative designs, registry-based randomized clinical trials (RCT), and dynamic global registries using RWD. Establishing partnerships and carrying out intricate trial designs may come at a high initial cost, but they guarantee long-term advantages including development more thorough, practical knowledge and developing appropriate MMD treatment guidelines and methods.

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