Chapter

Moyamoya Disease: A Rare Vascular Disease of the CNS

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Abstract

Moyamoya disease (MMD) is a rare disease affecting the cerebral vasculature of the central nervous system (CNS) with a reported incidence of 0.35–0.94 per 100,000 populations. It was first reported from Japan and later from other parts of the world. The pathology is narrowing of blood vessels supplying anterior circulation and rarely posterior circulation. It was believed that the disease is genetic in origin, but environmental factors also play a role. Patients with this rare disease may present with ischemic or hemorrhagic symptoms. Ischemic symptoms account for the disease in most of the pediatric patients, whereas in adults, hemorrhage is more common. Diagnostic imaging like CT angiogram and magnetic resonance angiogram helps in demonstrating the narrowing or the collateral vessels like "a puff of smoke" (moyamoya) formed at the base of the brain. Moyamoya disease is treated medically and/or surgically. Aspirin is the main medication used. Surgical options are direct or indirect revascularization techniques to bypass the stenosis. The disease is progressive in majority of the patients, but if treated early, they can have good prognosis especially children.

Keywords: moyamoya, vascular, CNS, MMD, MMS

1. Introduction

Moyamoya disease (MMD) is a rare disease of the central nervous system (CNS). It was first reported in Japan in the year 1957 and later reported from other Asian countries. "Moyamoya" in Japanese means "a puff of smoke" alluding to the characteristic angiographic appearance of the collateral circulation in the brain of the patient with moyamoya disease [1]. It can present either as an isolated condition (moyamoya disease) or as a part of a syndrome associated with other conditions. In the latter case, it is called moyamoya syndrome (MMS). Moyamoya disease usually manifests bilaterally [2], and moyamoya syndrome manifests, unilaterally, to begin with, which may progress to become bilateral disease [3].

2. Etiology

Ten to fifteen percent of moyamoya disease (MMD) is familial in origin which indicates a genetic association. East Asian populations with RNF213 gene on chromosome

17q25.3 are susceptible to MMD [4]. In another report from Japan, it was observed that a variant of RNF213 (c.14576G) was present in 41 patients with familial MMD (95%), 163 patients with sporadic MMD (79%), and 283 normal control subjects (2%) [5]. In a study in Chinese Han population, Wu et al. demonstrated that mutations in RNF213 gene were associated with increased susceptibility to MMD. In further analysis, they observed that ischemic MMD was related to the R4810K mutation, and hemorrhagic MMD was associated with the A4399T mutation [6]. Mineharu et al. suggested that MMD is an autosomal dominant disease with incomplete penetrance [7]. Inoue et al. observed that different alleles of genes of HLA antigen have been found to be associated with MMD [8]. Several inducers of angiogenesis such as fibroblast growth factor, transforming growth factor beta1, and hepatocyte growth factor which promote neovascularization were found in high levels in patients with MMD [9–11].

Moyamoya syndrome (MMS) is a different entity when the disease is associated with some other conditions such as [12]:

1. Atherosclerosis

2. Infectious diseases: meningitis and other viral or bacterial infections

3. Hematologic conditions: sickle cell disease, beta thalassemia, Fanconi anemia, hereditary spherocytosis, homocystinuria and hyper-homocysteinemia, factor XII deficiency, essential thrombocythemia

4. Vasculitis and autoimmune diseases: systemic lupus erythematosus, polyarteritis nodosa postinfectious vasculopathy, Graves' disease thyroiditis, Sneddon syndrome, antiphospholipid antibody syndrome, anti-Ro and anti-La antibodies

5. Type 1 diabetes mellitus

6. Connective tissue disorders and neurocutaneous syndromes: neurofibromatosis type 1 (NF1), tuberous sclerosis, Sturge-Weber syndrome, phakomatosis pigmentovascularis type IIIb, hypomelanosis of Ito, pseudoxanthoma elasticum, Marfan syndrome, chromosomal disorders

7. Chromosomal disorders: down syndrome, turner syndrome, Alagille syndrome

8. Other vasculopathies: vasospasm after subarachnoid hemorrhage, radiation therapy to the base of the brain, fibromuscular dysplasia

9. Other extracranial cardiovascular diseases: congenital heart disease, Williams syndrome, coarctation of the aorta, renal artery stenosis

10. Metabolic diseases: type I glycogenosis, hyperphosphatasia, primary oxalosis

11. Cranial trauma

12. Brain tumors

13. Cavernous malformation

14. Pulmonary sarcoidosis

15. Hereditary multisystem disorder with short stature, hypergonadotropic hypogonadism, and dysmorphism

16. Polycystic kidney disease

There are reports of identical twins with only one among them affected by MMD, which question the genetic basis and focus on environmental factors for the condition [13].

3. Epidemiology

Although originally reported in the Asian population, moyamoya disease has also been reported from Europe and America [1].

In an epidemiological study by Baba et al. [14], MMD was found to have the following characteristics in the Japanese population:

- Annual incidence of 0.35–0.94 per 100,000 populations
- A prevalence of 3.2–10.5 per 100,000 populations
- A male-to-female ratio of 1:1.8–1:2.2 reflecting a female predilection
- A family history of MMS in 10.0–15.4% of patients

Although the reported incidence of MMS from Washington and California was as low as 0.086 per 100,000 populations generally, in ethnic groups, it was found to be as high as 0.28 per 10,000 populations close to the incidence in Japan [15].

MMS shows a bimodal distribution in the Chinese population with a major peak in the 5–9-year-old group and another peak in the 35–39-year-old group [16]. In the Japanese population, there are two conflicting reports of higher peaks, one in childhood and another in adults [14, 17].

4. Clinical presentation

Patients affected by MMD present with ischemia like transient ischemic attack (TIA) and stroke and seizures or with intraparenchymal bleeds due to the rupture of fragile collateral vessels formed to compensate for the ischemia. They may also present with headache due to dilated transdural collateral blood vessels. A 2012 systematic review of population-based studies by Kleinloog et al. found that the predominant mode of presentation was ischemia, especially in children [18]. Ninety percent of children present with stroke and 7.5% present with TIA as per International Pediatric Stroke Study published in 2017 [19]. In children, exercise, crying, coughing, straining, fever, or hyperventilation can trigger symptomatic episodes of ischemia.

Adult patients in Japan with MMS mostly present with hemorrhagic stroke in some old reports [20] in contrast to patients from the United States in whom the ischemic stroke was found to be more common [21]. In a study done on 88 Korean patients, 45% of them had only a single ischemic or hemorrhagic stroke, 55% recurrent attacks mostly ischemic, and 64% of them presented with hemiplegia [22].

Ischemic symptoms of MMD are typically associated with the anterior circulation regions like frontal, parietal, and temporal lobes supplied by internal carotid

(ICA) and middle cerebral artery (MCA). Commonly the symptoms are hemiparesis, dysarthria, aphasia, and cognitive impairment [23]. Some patients may present with seizures, defective vision, syncopal attacks, or personality changes and can mimic psychiatric disorders [24]. Surgical patients undergoing minor procedures under anesthesia may present with perioperative stroke due to hyperventilation-induced cerebral vasoconstriction of the already compromised cerebral vasculature of the ischemic penumbra [25]. Patients with MMD can develop cerebral aneurysms at the tip of the basilar artery and the posterior communicating artery and present with subarachnoid hemorrhage [26].

Choreiform movements are another group of symptoms with which children can present due to the moyamoya-associated dilated collateral vessels in the basal ganglia [27]. Occasionally a characteristic ophthalmologic finding is seen in association with MMD identified as "morning glory disk," an optic disk enlargement with concomitant retinovascular anomalies [28].

5. Pathophysiology

In patients with this condition, large intracerebral arteries show a variable degree of stenosis and occlusions. Vascular intima shows fibrocellular thickening; elastic internal lamina will be tortuous, duplicate or triplicate; and the media show attenuation. Vessels may be dilated and thin-walled or thick-walled and stenosed in different regions. The hallmark of MMD is the meshwork of dilated vessels called moyamoya vessels (**Figure 1**). Aneurysms can form in some parts of cerebral vasculature as well.

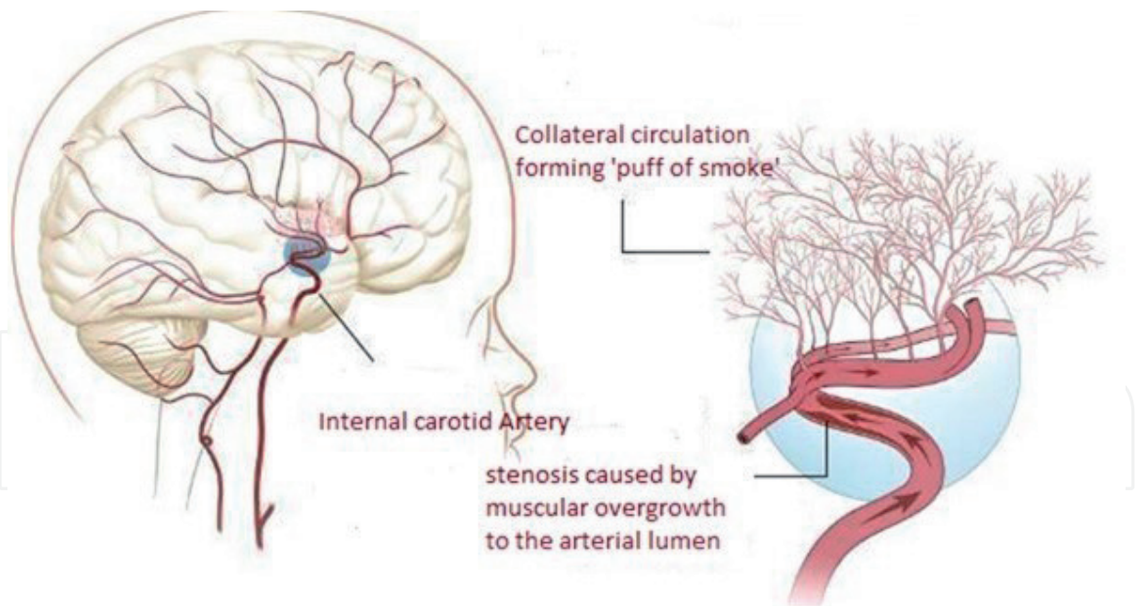

Figure 1.
Pathophysiology of moyamoya disease (modified from [29]).

6. Diagnostic radiology

Diagnosis can be established by invasive and semi-invasive radiological studies. At the bedside, transcranial Doppler (TCD) can detect stenosis of major arteries. Conventional CT or MRI helps to detect ischemic and hemorrhagic signs of MMD. CT angiography and conventional angiography are important to establish the exact point of narrowing in the circle of Willis.

Stage	Characteristics
Stage 1	• Narrowing of carotid fork only • Narrowed ICA bifurcation
Stage 2	• Initiation of basal moyamoya • Dilated ACA, MCA, and narrowed ICA bifurcation with moyamoya change
Stage 3	• Intensification of the "moyamoya" • Further increase in moyamoya change of the ICA bifurcation and narrowed ACA and MCA together with the reduction of flow
Stage 4	• Minimization of moyamoya vessels • Moyamoya change reducing with occlusive changes in ICA and tenuous ACA and MCA
Stage 5	• Reduction of moyamoya • Further decrease in moyamoya change with occlusion of ICA, ACA, and MCA (no flow)
Stage 6	• Disappearance of moyamoya vessels • The cerebral circulation is supplied only by the external carotid system

Table 1.
Suzuki staging system for moyamoya.

Suzuki and coworkers studied the angiographic progression of MMD and identified six stages (**Table 1**) of progression [1, 2].

This staging neither correlates with disease severity nor allows therapeutic risk stratification.

6.1 CT head

Cortical and/or subcortical infarction can be seen in the early stages, but in the later stages, dilatation of sulci or ventricles due to loss of volume can be seen. In a retrospective case series of 32 patients by Kim et al. [30], early stages (stages 1 and 2 of MMD) had mainly subcortical ischemic changes, whereas later stages (stage 3 and above) had cortical ischemic changes.

6.2 Magnetic resonance imaging

Diffusion and perfusion MR techniques are superior to CT scan for detection of subtle ischemic brain lesions especially in the acute condition. MRI was sensitive to detect watershed infarction in 50% of children as per a study done in Canada [31]. Dilated collateral vessels at the base of the brain are considered pathognomonic of MMD but seen only in some cases. In T2 sequences asymptomatic microbleeds may be seen. FLAIR images and T1 sequences may show a characteristic sign called ivy sign as in **Figure 2** (a linear pattern of increased signal in the leptomeninges and perivascular spaces) [33]. This is due to retrograde flow in leptomeninges resembling ivy creeping a stone. Magnetic resonance angiography (MRA) has surpassed conventional angiography in some centers as the primary imaging method although the latter is still considered as the gold standard.

6.3 Angiography

Conventional cerebral angiography is the gold standard for the diagnosis of MMD as it can clearly demonstrate the stenotic vessels in the anterior circulation as well as the collateral tuft of vessels formed (**Figure 3**). Apart from this, the small aneurysms which may be associated with MMD also can be detected in cerebral angiography.

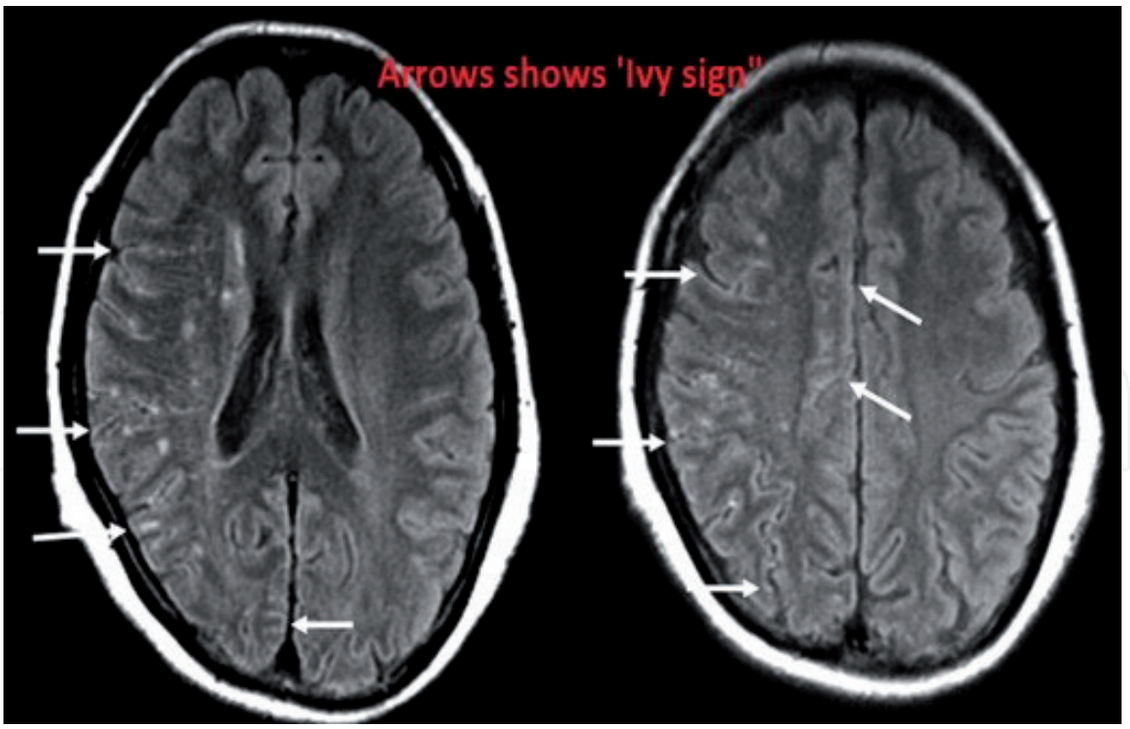

Figure 2.
FLAIR sequence showing ivy sign (modified from [32]).

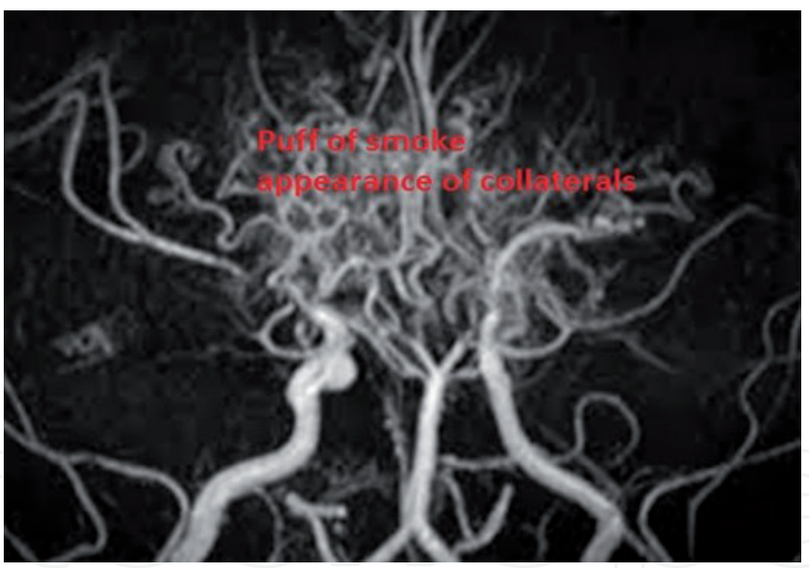

Figure 3.
Characteristic "puff of smoke" appearance in cerebral angiography.

6.4 Transcranial Doppler (TCD)

Stenosed vessels will have increased flow velocity proportional to the degree of stenosis, which can be detected noninvasively by TCD.

6.5 Electro encephalogram (EEG)

A specific pattern of hyperventilation-induced diffuse monophasic slow waves called "build-up" and post-hyperventilation "rebuild-up" waves similar to build-up waves in patients without MMD may be observed in patients with MMD [34].

Perfusion CT, xenon-enhanced CT, perfusion-weighted MRI, positron emission tomography (PET), and single-photon emission CT (SPECT) with acetazolamide challenge are other modalities rarely used in diagnosis [12].

7. Diagnostic criteria for MMD

A Japanese research group has put forward the following diagnostic criteria for the diagnosis of MMD [35]:

- Stenosis or occlusion at the terminal portion of the internal carotid artery and at the proximal portion of the anterior and middle cerebral arteries on magnetic resonance angiography (MRA).
- Abnormal vascular networks in the basal ganglia on MRA; these networks can also be diagnosed by the presence of multiple flow voids on brain MRI.
- Bilateral angiographic findings; although unilateral angiographic findings are considered probable.
- Conditions to be excluded:
    - Arteriosclerosis
    - Autoimmune disease
    - Brain neoplasm
    - A history of cranial irradiation
    - Down syndrome
    - Head trauma
    - Neurofibromatosis
    - Meningitis

8. Treatment of MMD

In the acute stage, treatment is symptomatic for those patients with ischemic or hemorrhagic stroke as per acceptable guidelines. It should be focused on treating elevated intracranial pressure, evacuation of hematoma, draining intraventricular hemorrhage by external ventricular drain (EVD), control of seizures, glycemic control, and treatment of fever.

In children diagnosed with MMD, crying and hyperventilation should be avoided as it can induce cerebral vasoconstriction. Pain management also should be taken care of. Supplemental oxygen also helps in avoiding hypoxia. Generally, hypotension, hyperthermia, hypoxia, hypocarbia, and hypovolemia should be avoided.

There are no interventions proved to improve outcome in MMD. The utility of thrombolysis has not been studied yet and may be risky due to the possibility

of development of hemorrhage from the fragile collateral vessels [36]. Aspirin has been recommended by the American College of Chest Physicians (ACCP) for children with ischemic stroke [37].

There were no significant differences in outcome between medically and surgically treated patients with MMD as per a large survey from Japan, but a later review revealed that 38% of 651 patients with MMD who initially underwent medical management ultimately had to go for surgery because of progressive symptoms [38].

8.1 Secondary stroke prevention

Treatment of underlying diseases like sickle cell disease is helpful in secondary prevention. Surgical revascularization is the mainstay of secondary prevention. Antiplatelet medications like aspirin have an important role in preventing stroke in mild disease or asymptomatic patients who are at high risk for surgery [39]. Oral anticoagulants are not helpful as they can increase the chance of hemorrhage. Calcium channel blockers were used in some reports [40]. Endovascular embolization has been used for the obliteration of aneurysm associated with MMD.

9. Surgical management of moyamoya disease

The aim of surgical management of moyamoya disease is to vascularize and restore the blood supply by bypassing the stenosed area. It will stabilize the cerebrovascular hemodynamics. It prevents bleeding by preventing the progression of the thin moyamoya vessels. Improvement and or normalization of cerebral hemodynamics by the surgical intervention will also prevent secondary stroke prevention and improve the neurological and neurocognitive outcome.

Revascularization surgery is the most effective treatment for hemorrhagic MMD [41] and can be effective in preventing future stroke events in adults [42].

The main indications for the surgical interventions are cerebral hemodynamic impairment and repeat ischemic symptoms. The severity of the disease to assign a patient for surgical intervention can be made by the Berlin moyamoya grading system (**Table 2**). But the literature has not mentioned the severity at which there is an indication for surgical intervention.

Variable	Characteristics	Points
Digital subtraction angiography	Steno-occlusive lesion + moyamoya vessels	1
	Steno-occlusive lesion + moyamoya vessels + intracranial compensation routes	2
	Steno-occlusive lesion + extracranial compensation routes	3
MRI	No signs of ischemia, hemorrhage, or atrophy	0
	Signs of ischemia, hemorrhage, or atrophy	1
Cerebrovascular reserve capacity	No steal phenomenon (≥5%)	0
	Steal phenomenon (<5%)	2

Table 2.
The Berlin moyamoya grading [43].

10. The Berlin moyamoya grading

It incorporates digital subtraction angiography (DSA), MRI, and cerebrovascular reserve capacity (CVRC) which gives the information of the functional cerebrovascular assessment of hemodynamic impairment [43].

It was proposed by Czabanka et al. According to the grading system, there are three grades:

1. Grades 1–2: mild
2. Grades 3–4: moderate
3. Grades 5–6: severe

11. Indications for surgical revascularization

Patients with ischemic symptoms and progressive disease with impairment in cognition benefit from surgical revascularization methods. It can be achieved by direct and indirect methods.

11.1 Direct surgical treatment

A branch of the external carotid artery is connected to the branch of the internal carotid artery beyond the stenosis to bypass the stenosed segment. Superficial temporal artery to middle cerebral artery (STA-MCA) (**Figure 4**) bypass is the commonly used technique [45]. Other less common direct techniques are STA-ACA, STA-PCA, and occipital artery-PCA anastomosis. These direct techniques are used when an immediate recirculation is indicated. The major drawback is that this cannot be easily done in children with MMD because of the smaller size of donor and recipient arteries.

11.2 Indirect surgical treatment

In this technique, a vascularized tissue supplied by the external carotid artery (e.g., dura, temporalis muscle, or the superficial temporal artery itself) is placed in direct contact with the brain surface, which results in ingrowth of new blood vessels to the underlying cerebral cortex (**Figure 5**). In this technique, good cerebral blood flow is established after a few weeks and so not suitable for emergency cases [46], but good for pediatric patients with MMD because of the lower technical difficulty. The following are the options for indirect revascularization [47]:

- Encephaloduroarteriosynangiosis (EDAS) and its modification called pial synangiosis
- Encephalomyosynangiosis (EMS)
- Encephalo-duro-arterio-myosynangiosis (EDAMS)
- Encephaloarteriosynangiosis
- Encephaloduroarteriosynangiosis
- Omental transplantation

- Craniotomy with inversion of the dura
- Multiple burr holes without vessel synangiosis
- Cervical sympathectomy

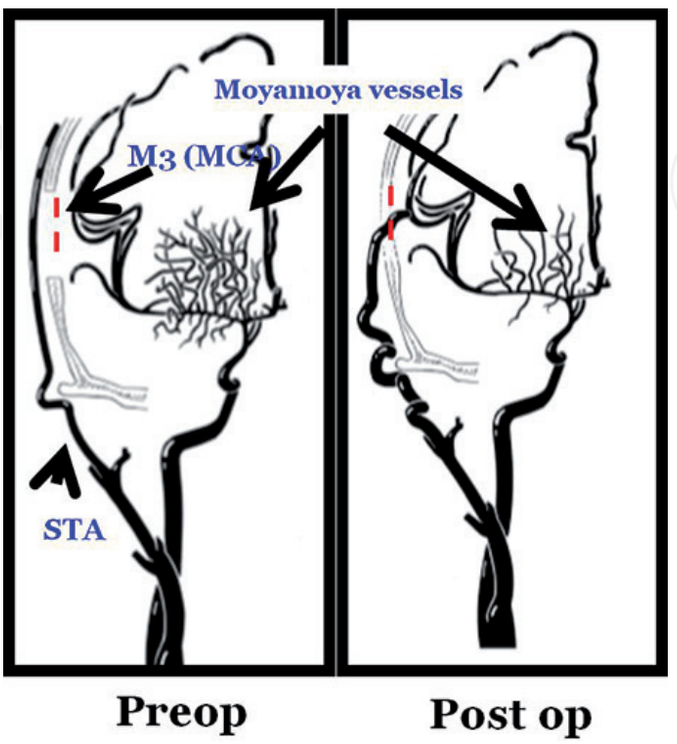

Figure 4.
Direct bypass procedure of superficial temporal artery (STA) and M3 branches of the middle cerebral artery (MCA) (modified from Acker et al. [44]).

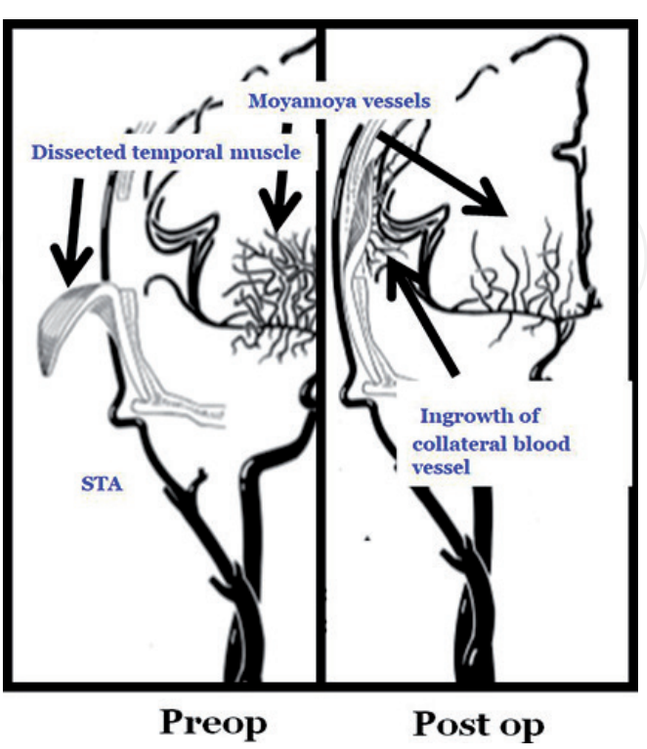

Figure 5.
Indirect bypass procedure of indirect bypass procedure: dissected temporal muscle on the brain surface (modified from Acker et al. [44]).

11.3 Combined techniques

Houkin et al. first performed a combined revascularization surgery. It combined the superficial temporal artery and M3 branches of the middle cerebral artery (STA-MCA) bypass and encephalo-duro-arterio-myosynangiosis (EDAMS) (**Figure 6**). The aim of the combined procedure is to improve the results to serve as an alternative in case the direct bypass fails and prevents second surgery. The direct bypass immediately improves the hemodynamics [44]. A 2005 systematic review from Japan compared direct, indirect, and combined techniques and found that there is no statistically significant difference between all these techniques in terms of outcome during 58 months of follow-up period [48]. Efficacy of medical and surgical management was also compared in a large survey conducted in Japan and concluded that there is no significant difference between the two [49]. However, in another study, it was found that children initially underwent medical therapy had to ultimately go for revascularization surgery more than the children who underwent surgery in the first instance [38].

11.4 The complication of the surgical revascularization

Surgical revascularization is not risk-free. This can range from a transient increase in intracranial pressure resulting in headache, seizures, and reversible neurological deficits to perioperative stroke. The mechanism is cerebral hyperperfusion syndrome because of the revascularization-induced hyperperfusion of the area supplied by the chronically vasoconstricted blood vessels, where the autoregulation is impaired. Incidence of this phenomenon was found to be up to 47% [50].

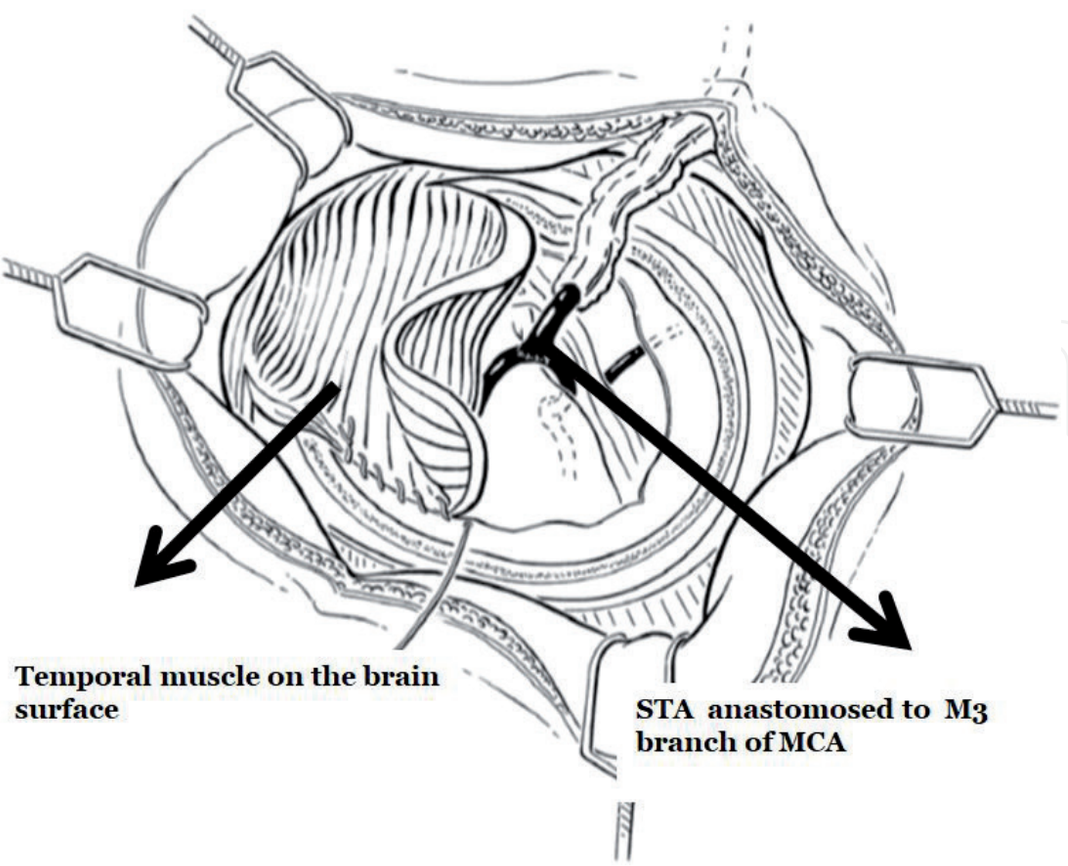

Figure 6.
Combined revascularization procedure. The temporal muscle is positioned on the brain surface, and the STA is a bypass graft to the M3 branch of MCA (modified from Acker et al. [44]).

All adults and children with ischemic MMD or MMS should have aspirin for a long term. If there are no contraindication and significant ischemic symptoms, surgical revascularization is a reasonable option [47]. AHA guidelines recommend it for patients with compromised cerebrovascular perfusion according to blood flow studies [39]. As mentioned before there is no evidence for opting for direct or indirect revascularization or vice versa, though the latter is preferred in the pediatric age group. Evidence for postoperative use of aspirin is limited. In a recent retrospective study, patients treated with postoperative aspirin had better outcome [44, 51].

12. Prognosis

Prognosis depends on how fast the blockage occurs and how effective the collateral circulation is established. Fifty to sixty-six percent of patients will have the progression of the disease, and they have a poor outcome. Pediatric patients who were surgically treated were found to have disease progression in an estimated 2.6% of patients only. Among untreated asymptomatic patients, the annual stroke rate was found to be 3.2% and disease progression in 80% [52, 53].

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