Moyamoya Disease (MMD)

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Abstract: Moyamoya disease (MMD) is a progressive occluding intracranial carotid artery disease, which can be either unilateral or bilateral. Here, the anterior circulation is commonly involved. In the center core, there is development of a profuse thin wall capillary known as moyamoya vessels. MMD is among the most common causes of neurological morbidity and disability in children. In children, it usually presents with ischemia and infarct, whereas in adults, it presents with hemorrhage. A CT scan of the head, an MRI of the brain, CTA and MRA are the necessary investigation methods, whereas a cerebral DSA is the gold standard. Perfusion images are important for follow up. Treatment includes cerebral revascularization by a direct or indirect bypass, or in combination. In this chapter, the etiopathogenesis, clinical features, investigation methods and management of MMD will be discussed.

Abbreviations

ACA	anterior cerebral artery	CBF	cerebral blood flow
CVR	cerebrovascular reservoir	ECA	external carotid artery
EDAS	Encephaloduroarterio synangiosis	EDMAS	encephaloduromyoarterio synangiosis
EDMAPS	encephaloduromyoarteriopial synangiosis	EMS	encephalomyosynangiosis
EGS	Encephalogaleosynangiosis	ICA	internal carotid artery
ICH	intracerebral hemorrhage	ICP	intracranial pressure
MCA	middle cerebral artery	MMD	moyamoya disease
NF	Neurofibromatosis	OA	occipital artery
PCA	posterior cerebral artery	STA	superficial temporal artery
TIA	transient ischemic attack		

1. Introduction

Moyamoya disease (MMD) is a rare variety of congenital vascular abnormalities where there is progressive occlusion of the intracranial carotid artery, which is either unilateral or bilateral. The progressive bilateral spontaneous occlusion of ICAs with compensatory capillary collaterals look like a "puff of smoke" (Japanese: moyamoya) on angiogram (Figure 1). It is a progressive disease where the anterior circulation, such as the supraclinoidal carotid artery, is usually involved. Hence, the large area becomes ischemic. In the center core, there is development of a profuse thin wall capillary known as moyamoya vessels. MMD is among the most common causes of neurological morbidity and disability in children due to cerebrovascular illness, such as cognitive and motor dysfunctions. According to previous research, infants have a higher frequency of ischemia pathophysiology due to insufficient perfusion, whereas adults have a higher prevalence of bleeding due to the fragility of neovessels (Kirollos et al. 2019).

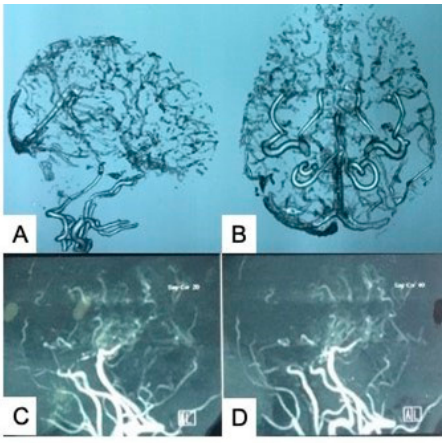

Figure 1. (**A**,**B**) CTA showing moyamoya vessels; (**C**,**D**) MRA showing moyamoya vessels. Source: Figure by authors.

2. Moyamoya Syndrome-Associated Diseases

- Sickle cell anemia
- Neurofibromatosis type I
- Past cranial radiation therapy
- Trisomy 21
- Primary dwarfism
- Congenital cardiac diseases
- Giant cervicofacial hemangiomas and PHACE syndrome
- Renal artery stenosis
- Alagille syndrome
- Hyperthyroidism
- (PHACE—posterior fossa abnormalities, hemangioma, arterial lesion, cardiac abnormalities and/or artic coarctation and eye abnormalities) (Greenberg 2010).

3. Epidemiology

MMD was first discovered in Asian patients, although it has now been observed in people of various races and ethnicities. The precise number of incidents is unknown. According to Japanese studies, the yearly incidence is between 0.35 and 0.94 per 100,000 people, and the yearly prevelence is 3.16–10.5 per 100,000 people. In comparison to males, females have a twice-as-high rate (July and Wahjoepramono 2019).

3.1. Types

The Ministry of Health and Welfare of Japan categorized MMD according to its manifestation into four types:

a. Ischemic;
b. Hemorrhagic;
c. Epileptic;
d. Others.

At a pediatric age, the ischemic type is the most common, and in adults, the hemorrhagic type is the most common.

3.2. The Suzuki Stages

The Suzuki stage (July and Wahjoepramono 2019) appears to correlate with collateralization in children, but not in adults.

Stage I

- "Narrowing of the ICA fork"
- Narrowed ICA termination.

Stage II

- "Beginning of the moyamoya";
- Dilated MCA and ACA, as well as narrowed ICA termination with moyamoya alteration.

Stage III

- "Intensification of the moyamoya";
- Further increases in moyamoya change of the ICA termination with a narrowed ACA and MCA.

Stage IV

- "Minimization of moyamoya";
- Moyamoya change decreasing with occlusive alterations in the ICA with a tenuous ACA and MCA.

Stage V

- "Decreasing of moyamoya";
- Further decreases in moyamoya change with occlusion of the ICA, ACA and MCA.

Stage VI

- "Disappearance (lost) of moyamoya";
- ICA essentially disappears and the brain is supplied by the ECA.

Posterior circulation is usually not affected by MMD; however, it can be affected, too. Usually, the development of MMD peaks at two ages: childhood and adulthood; often it presents as either ischemic features or hemorrhagic manifestation, and sometimes seizure disorder. Often, patients suffer for a long period of time before arriving to seek medical attention. Any form of an angiogram is the diagnostic method for MMD. We usually employ a CT angiogram or MR angiogram as the first-line investigation method for MMD (Kirollos et al. 2019).

Because juvenile MMD is more likely to advance than adult MMD, revascularization surgery is recommended for the majority of children with MMD. As a result, in order to attain a positive clinical result in children, an early diagnosis and active intervention are critically needed before irreparable brain damage (Figure 2) happens. As previously stated, the risk of stroke in silent MMD patients or those with MMD who have a relatively stable circulatory condition appears to be high (Kirollos et al. 2019; Zhang et al. 2021).

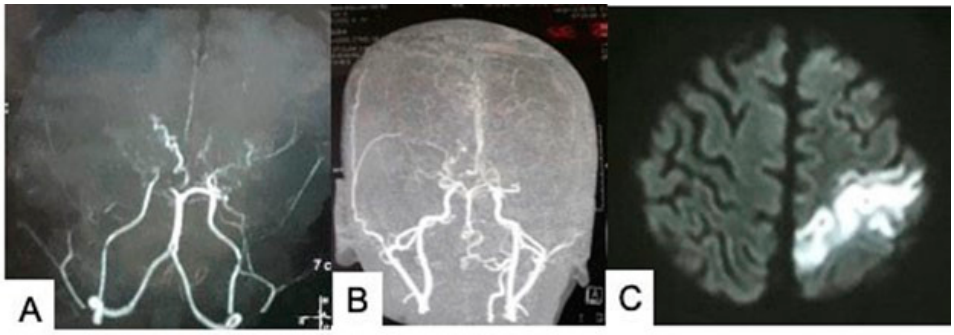

Figure 2. Bilateral supranclinoidal carotid artery occlusion (**A**,**B**) and high signal intensity along the motor strip due to ischemia (**C**). Source: Figure by authors.

4. Treatment

4.1. Surgical Revascularization

- Direct revascularization
- Indirect revascularization
- In combination

4.1.1. Indication of Surgery

- ICH;
- Symptomatic ischemia or transient ischemic attack (TIA);
- Cognitive impairment;
- Decreased CBF and/or CVR;
- Selective asymptomatic cases (ivy sign on MRI) (50% progress within 5 years).

One of the common indications of surgery is multiple episodes of a TIA. The aim of surgery is to preclude further events by re-establishing enough blood supply to the involved brain (Kirollos et al. 2019; Zhang et al. 2021; Katsumi 2019; Macdonald 2008; Nader et al. 2013).

Perioperative management principles in MMD patients are listed in Table 1.

Table 1. Perioperative management guidelines for moyamoya patients.

Time	Guidelines
At 1 day before operation	Continuation of aspirin therapy (generally 81 mg daily per oral if weight <70 kg and 325 mg daily per oral if weight $\geq$70 kg);
	Admission of patient for overnight intravenous fluid hydration (isotonic saline 1.25–1.5$\times$ maintenance).

Table 1. *Cont.*

Time	Guidelines
At induction of anesthesia	Commencement of EEG monitoring;
	Maintenance of normal BP during induction of anesthesia and normal temperature (particularly in smaller children), normal PCO2 (eliminate hyperventilation to reduce vasoconstriction, PCO2 > 35 mm Hg) and normal blood PH;
	Installment of extra intravenous channels, arterial channel, urinary catheter and a pulse oximeter;
	Placement of precordial Doppler (for venous air embolus surveillance).
During surgery	Maintenance of normocarbia, normotension, normothermia, normal pH, enough hydration and adequate oxygenation;
	Slowing of EEG tracing may respond to sequential BP increases or other techniques to improve the CBF.
Postoperatively	Avoidance of hyperventilation (equivalent with crying in pediatric age), analgesia is vital; Maintenance of aspirin on postoperative day 1;
	Maintenance of intravenous fluid at 1.25–1.5× maintenance until the patient is completely recovered and drinking enough (frequently from 48 to 72 h).

Source: Authors' compilation based on data from Kirollos et al. (2019).

4.1.2. Surgical Methods

A. Direct arterial bypass:

- STA–MCA;
- STA–ACA;
- OA–PCA.

B. Indirect:

- EDAS;
- EDAMS;
- EMS;
- EDMAPS;
- Pial synangiosis;
- Omental synangiosis;
- Multiple burr hole.

Different techniques that are used for indirect revascularizations in MMD are listed in Table 2.

Table 2. Different tissues (techniques) that are used for indirect revascularizations.

Different Tissues	
1.	Techniques utilizing the galea
2.	Techniques utilizing the scalp artery
3.	Techniques utilizing the temporal or other muscles
4.	Techniques utilizing the dura mater
5.	Techniques utilizing a combination of the above
6.	Techniques utilizing the omentum
7.	Direct and indirect anastomoses (combined)

Source: Table by authors.

C. Both direct and indirect methods: We commonly employ both direct and indirect methods of a brain bypass for moyamoya disease for both ischemic and hemorrhagic cases. A direct bypass is performed with the STA and MCA M4 branch. It is better to perform a more direct bypass, preferably two bypasses via the frontal and parietal branches.

4.1.3. Bypass Surgery in MMD for Cerebral Revascularization

Cerebral bypass surgery involves the use of grafts to revascularize either an extracranial vessel and an intracranial vessel or an intracranial artery, as well as another intracranial artery (radial artery, saphenous vein, etc.). The goal of a bypass is to restore or redirect blood flow from a restricted, obstructed or damaged channel to the distal portion of the artery. It is fairly typical to simply use the natural supplied artery, such as the STA, and bypass it entirely to reach the MCA (Katsumi 2019).

Direct Cerebral Bypass for MMD

The term "direct bypass" refers to an anastomosis of the superficial temporal artery (STA) to the middle cerebral artery (MCA), which can enhance cerebral perfusion in surgical areas almost instantly (Figures 3 and 4). Other direct methods are STA–ACA and OA–PCA bypasses.

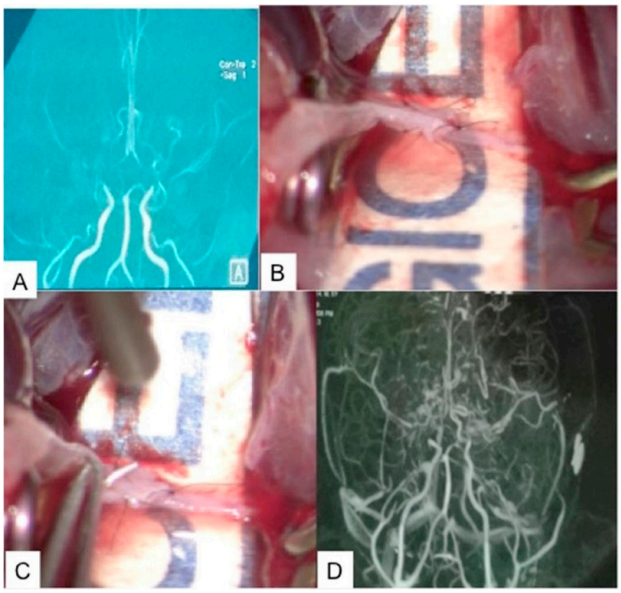

Figure 3. (**A**) MRA of the brain showing bilateral MMD in a 4-year-old child; (**B**,**C**) preoperative pictures of a direct STA–MCA bypass; (**D**) postoperative CTA on the first POD of the brain showing increased vascularity of the brain. Source: Figure by authors.

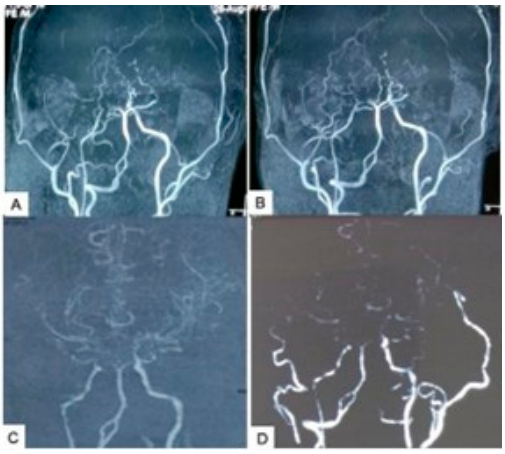

Figure 4. (**A**,**B**) Preoperative CTA of the brain in an adult with bilateral symptomatic MMD; (**C**,**D**) postoperative CTA on the first POD showing a direct STA–MCA bypass with increased parenchymal vascularity. Source: Figure by authors.

Indirect Cerebral Bypass for MMD

There are verities of indirect cerebral bypasses that include encephalomyosynangiosis, encephaloduroarteriosynangiosis, ribbon encephaloduroarteriomyosynangiosis, the multiple burr hole surgery technique, encephaloduromyoarteriopericraniosynangiosis, omentum transplantation, etc.

a. EDAS (Encephaloduroarteriosynangiosis): EDAS surgery is an indirect way of establishing new arterialization in the brain. It uses the STA which is dissected free from the adjacent soft tissue and then put directly on the cortical surface.
b. Encephalogaleo synangiosis (EGS): In the ACA region, a bifrontal EGS with a craniotomy showed better angiogenesis and an improved CBF. It is thought to be a straightforward, safe and successful surgical treatment for improving ischemia in the ACA area in pediatric patients.
c. Encephalomyosynangiosis (EMS): The encephalomyosynangiosis (EMS) operation is an indirect revascularization technique where the temporalis muscle is divided and transferred onto the surface of the brain through a hole in the skull. Between blood-rich muscle and the brain, new veins emerge throughout time.
d. Encephaloduroarteriomyosynangiosis (EDAMS): EDAMS surgery is a summation of simultaneous EDAS and EMS.
e. Multiple burr hole: In the management of MMD in children, many burr holes and arachnoid apertures are formed over both cerebral hemispheres (Figure 5).

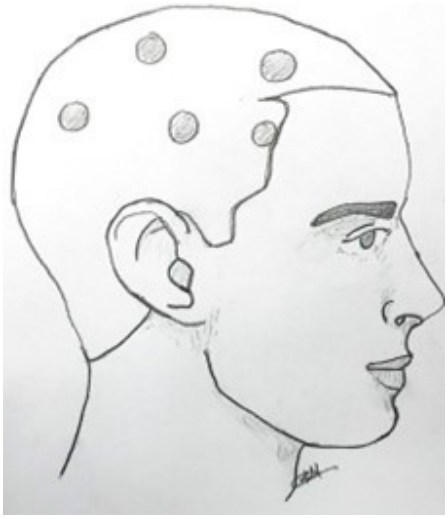

Figure 5. Revascularization through burr holes. Outline of the burr hole sites (2-to-4) to achieve indirect revascularization. Source: Figure by authors.

The most favorable feature of direct revascularization is the immediate increase in blood flow. Delayed synangiosis is also a possibility. Direct cerebral revascularization, on the other hand, is a more difficult technique with a lengthier learning curve than indirect cerebral revascularization.

4.1.4. Complications of Cerebral Revascularization in MMD

Scalp avascular necrosis is not an uncommon complication. When the STA and its branches are taken for a bypass, it may affect scalp blood supply due to rough dissection during the harvesting of the STA. Increased intracranial pressure (ICP) is a sign of hyperperfusion syndrome, which is caused by a rapid increase in cerebral blood flow. The complication of hyperperfusion syndrome has been described in patients managed for MMD, mostly adults and those managed with the direct cerebral revascularization method.

This necrosis usually needs regular dressing and sometimes plastic surgical intervention for correction.

Failed direct (i.e., STA–MCA) bypass which may have manifested in the form of increased weakness of the limbs or new development of hemiparesis.

Failure of an indirect bypass.

Intracerebral hemorrhage.

Surgical therapy for MMD should be explored for symptomatic patients due to the disease's progressive nature. An early diagnosis and prompt treatments are required for young patients before irreparable brain damage occurs. Surgical revascularization is an efficacious therapy for ischemic or hemorrhagic stroke prevention.

4.2. Conservative Treatment

Conservative treatments is used in incidental cases, with follow up to see any progression.
Drug therapy for moyamoya disease (efficacy is not known):

- Aspirin;
- Beta blocker;
- Ca chanel blocker (amlodipine).

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