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REVIEW ARTICLE

A Clinical Review on Moyamoya Disease Management

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ABSTRACT

Moyamoya disease (MMD) is a rare and unique cerebrovascular disease. The term "moyamoya" is Japanese and refers to a hazy puff of smoke or cloud. In people with moyamoya disease, this is how the blood vessels appear in the angiogram. MMD is characterized by the progressive stenosis of the distal internal carotid artery (ICA) resulting in a hazy network of basal collaterals called moyamoya vessels. This may be a consequence of Mutations in a few genes. In addition, MMD is also associated with many genetically transmitted disorders, including neurofibromatosis, Down syndrome, Sickle cell anemia, and Collagen vascular disease. It follows bimodal age distribution. Younger populations present with ischaemic symptoms, whereas adults show hemorrhagic symptoms The exact cause remains unknown. Immune, genetic and other factors contribute to this disease. It follows complex pathophysiology resulting in neovascularization as a compensatory mechanism. Diagnosis is based on cerebral angiography using the DSA scale. Treatment involves managing symptoms with medicine or surgery, improving blood flow to the brain, and controlling seizures. Revascularization helps to rebuild the blood supply to the underside of the brain.

KEYWORDS

Moyamoya disease, intracarotid artery, cerebrovascular, ischemia, haemorrhage, seizures, revascularization

INTRODUCTION

Moyamoya disease (MMD) is a unique cerebrovascular disease characterized by the progressive stenosis of the distal internal carotid artery (ICA) that results in a hazy network of basal collaterals called moyamoya vessels. It is of unknown etiology. The diagnosis is based on angiographic findings. The angiographic findings differ according to the stages of MMD.

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But sometimes these angiographic findings may not be sensitive. Therefore the current diagnosis is based on the presence of basal collaterals. [1,2]

Higher incidents are seen in the Asian population compared to the European and North American populations. There are 2 clinical signs of moya moya disease -1. Cerebral ischemia, 2. Cerebral hemorrhage. These differ in the pediatric and adult populations. In most, pediatric transient cerebral ischemic attacks and cerebral infarctions are seen along with mental decline and seizures. Whereas in adults 50 percent population experience intracranial hemorrhage and the remaining 50 may experience an ischaemic stroke.[3]

Studies have shown that approximately 10% of the population has genetically inherited this disease. Mutations in few genes may cause MMD. In addition, MMD is also associated with many genetically transmitted disorders, including neurofibromatosis, Down syndrome, sickle cell anemia, and collagen vascular disease.[1,4,5,6,7]

HISTORY

MMD was first described in Japanese literature by Takeuchi and Shimizu in 1957 as a case of "hypoplasia of the bilateral internal carotid arteries."[8] It was first published in English literature by Kudo, who described it as a "spontaneous occlusion of the circle of Willis" in 1968.[9] The popular terminology "MM" was suggested soon after in 1969 by Suzuki and Takaku. "MM" is a Japanese expression that refers to "something hazy, like a puff of cigarette smoke drifting in the air." Suzuki and Takaku coined the term MM to describe the characteristic angiographic appearance of the dilated collateral arteries that develop at the base of the brain.[8]

NEUROANATOMY

The brain receives blood supply from anterior and posterior circulation.

1. Anterior circulation receives blood from the internal carotid artery and supplies it to the cerebral hemisphere [frontal, parietal, temporal lobes]

2. Posterior receives from vertebral arteries and supplies to the hindbrain [brain stem, cerebellum, occipital lobe, and posterior part of cerebral hemisphere]

The posterior and anterior blood vessels connect and form an anatomical structure called the "circle of Willis"

1. **Structure:** The anterior communicating artery connects with the bilateral anterior cerebral artery these further connect to inter carotid artery, which runs into the brain through the neck. The inter carotid artery intersects with the anterior cerebral artery and the remaining inter carotid artery forms the middle cerebral artery. Posteriorly this middle carotid artery is connected to the posterior cerebral artery via the posterior communicating artery. The basilar artery is formed by the fusion of the posterior cerebral artery. These then divide into the vertebral artery and further gives rise to the single anterior spinal artery.[10]

2. **Function:** The function of the cow is to provide blood flow between the anterior and posterior regions of the brain and to protect against ischemia and other blood vessel diseases.[11]

EPIDEMIOLOGY

Most common in Asian countries like china, japan, and Korea. in japan prevalence was 3.16 per 100,000 in 1994, which raised to 10.5 per 100,000 in 2006. The US and Europe have one-tenth of prevalence compared to that of Japan. Females are twice as prone compared to males. Age-wise it is seen in either pediatrics (5-10 yrs) or adults (25-49yrs) this is called bimodal age distribution. The younger population shows ischaemic symptoms, whereas adults show hemorrhagic symptoms.[12]The presence of genetic susceptibility has been shown to play role in existing data.[13]

GENETIC ASSOSCIATION

According to a Japanese study, 5 different chromosomal regions are associated: 3p24-p26, 6q25, 8q23, 12p12, and 17q25.

1. **RNF213 as a susceptible gene for MMD :**

Also known as ring finger 213 is identified as the strongest gene for MMD. The studies show that there are two variants of the RNF213 gene. They are, PR4810KRNF213 variants are related to the ischaemic type of MMD while non-

PR4810KRNF213 is related to haemorrhagic type. [1,4,5,6,7]

2. **Pathophysiology according to gene involvement:**

RNF213 causes cerebral hypoxia by insufficient angiogenesis.
Data suggest that it is not an inflammatory disease but still inflammation plays an important role.(fig.1)
RNF213 is also associated with vascular risk like HTN resulting in hemodynamic stress. [1]

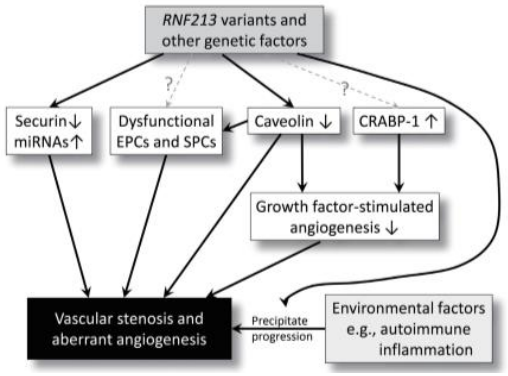

Fig.1 Pathophysiology according to gene involvement [1]

ETIOLOGY

The exact cause is not known. It is genetically inherited. Immune, genetic and other factors contribute to this disease. Inflammation plays a role.[14]
Inherited conditions and/or association:

- Sickle Cell Disease or trait
- Down Syndrome (Association)
- Neurofibromatosis type 1 (Association)

Acquired conditions:

- Head and/or neck irradiation
- Chronic meningitis
- Skull base tumor
- Atherosclerosis of skull base arteries
- Arteriosclerosis
- Cerebral vasculitis [15]

PATHOPHYSIOLOGY

This is a complex process. The pathophysiological features of the stenotic segment are the presence of microcellular thickening of the intima, irregularities in an elastic lamina, medial thinness, and a decreased outer diameter. There is a proliferation of endothelial cells and stenosis as a result of fibrocellular thickening of intima. Neovascularization is seen as a result of an increase in stenotic segment. Neovascularization is a compensatory mechanism for decreased cerebral blood flow. The new vessels formed are known as moyamoya vessels. It is an active process. They have dilated perforating arteries characterized by pathological findings like fibrin deposits in walls, fragment elastic lamina, attenuated media, and formation of aneurysms. [1] Recent studies have also shown the involvement of progenitor cells and circulating stem cells in the pathogenesis of MMD. [13]

CLINICAL PRESENTATION

Symptomatology in MMD is related to the compromised blood flow to the cerebral hemisphere and its consequences. The most common symptom thus is an ischemic stroke, and the signs vary according to the vascular territory affected. Anterior circulation is more often affected than posterior circulation.

The MM vessels which develop in response to stenosis of ICA are small in caliber and under hemodynamic stress. They are vulnerable and prone to bleed. Microaneurysms tend to develop in these vessels, and these aneurysms can rupture under stress. The incidence of aneurysms in MMD varies from 1% in children to 6.2% in adults.[9] Thus, the second common presentation in MMD is a cerebral bleed. Dilation of meningeal and leptomeningeal collateral vessels can result in headache.

Chronic infarcts with resultant gliosis can also result in seizures, focal deficits, and involuntary movements [Figure 2]. Chronic global hypoperfusion can result in a progressive decline in neurocognitive function. Involvement of the

posterior circulation territory may result in visual field defects, diplopia, scintillating scotomas, ataxia, and vertigo.[8]

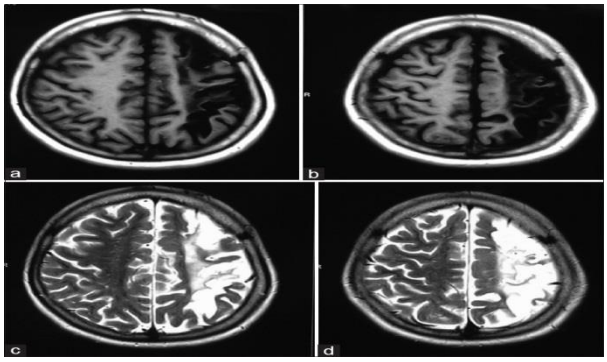

Figure 2: A 12-year-old female child with recurrent left hemispheric ischemic events. Magnetic resonance imaging axial T1 (a and b) and T2 (c and d) images showing extensive left hemispheric infarcts with gliosis

bleeding is more common in adults [Figure 3].[16-17][1] One characteristic feature in children is that ischemic events get precipitated by strenuous events, such as coughing, crying, hyperventilating, or blowing. Hypocapnia-induced vasoconstriction, accompanied by a transient reduction in cerebral blood flow (CBF) in an already compromised cerebral circulation, is responsible for these events.[18] Cerebral hemorrhage is more common in adults. Hemorrhage is the presentation in 40%–65% of adult patients, and the common locations are the basal ganglia (40%), thalamus (15%), or ventricular system (30%).[19-20] Metastatic carcinoma is also seen.[21] Younger population shows ischemic symptoms, where as adults shows hemorrhagic symptoms.[12] Growth hormone deficiency, Headache, Hemorrhagic stroke, Transient ischemic attack are also few symptoms. [21]

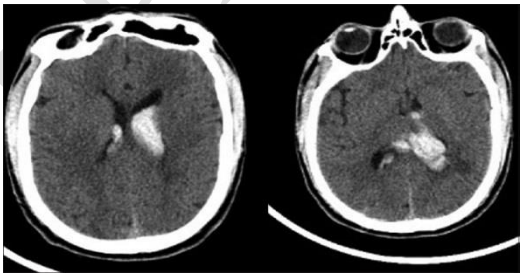

Figure 3: Computed tomography scan plain images of a 40-year-old male presenting with sudden-onset headache and altered sensorium. Scan images showing primary intraventricular haemorrhage

DIAGNOSIS

Diagnosis is based on cerebral angiography. Japan has made guidelines for MMD in the year 1996, based on angiographic findings, and is as follows

1. Anterior cerebral artery and medial cerebral artery occlusion.
2. Abnormal vascular network.
3. Bilateral manifestation.[3,22]

The recent guidelines were received in 2012 and remained the gold standard. The below figures show the staging of MMD (table.1) according to digital subtraction angiography [DSA].[23]

Table. 1 staging of MMD

stage	Angiographic description
1	Narrowing carotid fork.
2	Initiation of disease, collateral vessels is seen faintly, no direct collateral from ECA to ICA.
3	Intensification of disease, collateral vessels are seen clearly, stenosis.
4	Occlusion of ICA and may extend to PCoA and PCA. Minimization of moya moya.
5	Reduction of moya moya, extend of occlusion increases and collateral circulation increases.
6	Disappearance of moya moya, disappearance of cerebral circulation from ICA.

The MRA results are evaluated by adding the scores and then staging. A score of 0-1 represents stage 1 (DSA stage 1 and 2), A Score of 2-4 represents stage 2 (DSA stage 3), A Score of 5-7 represents stage 3 (DSA stage 4), A Score of 8-10 represent stage 4 (DSA stage 5 and 6).[3,22,23]

MANAGEMENT

1. Pharmacotherapy

Calcium channel blockers (nimodipine, verapamil, nicardipine, etc) were given for

symptomatic treatment. Studies showed no further episodes of transient ischemic attacks, seizures, or headaches in patients. Studies show nicardipine may have a beneficial effect on cerebral hemodynamics and may prevent ischemic sequelae from optimizing existing collateral circulation.[24] Additionally, antiplatelets and antiepileptics may also be used for MMD associated seizures disease. Drug therapy is usually ineffective and has only a symptomatic effect, revascularization surgery is the only option.[25]

2. Non-pharmacological management

Maintain spco2 levels between 35-40 mmHg. During direct arterial bypass measures like mild hypothermia (33-35degree centigrade) are maintained. Barbiturates are used to maintain mild HTN.[26-27] They are 3 types of surgeries currently available.

3. Direct vascularization :

In this technique, STA is connected to MCA. It has the benefit of immediately increased blood flow compared to indirect vascularization. This is preferred usually in adults.[28]

STA-MCA bypass: parietal branch of STA is taken as a donor and the posterior branch of MCA as the recipient's vessel. Sometimes anterior branch can be taken as donor and M2 as a recipient. Papevarin is used preoperatively for dilating arteries. And is irrigated post-operatively. Aspirin 325mg/dl is administered post-operatively.[25] Few cases present with hemorrhagic stroke with dangerous choroidal anastomosis on cerebral angiography.[29]

4. Indirect revascularization :

Usually done in children(presence of small arteries). As the name specifies this procedure is indirect and relies on the subsequent formation of collateral vessels. To enhance blood delivery, They don't provide immediate revascularization and hence delayed blood flow is a drawback.[25] This further includes :

i. ENCEPHALOMYSYNANGIOSIS: In this technique, temporal muscle is implanted on the lateral surface of the brain, and suturing is done in place to the dural edge.

ii. PIAL SYNOPSIS: It involves opening of arachnoid along with dural and suturing with STA.

iii. ENCEPHALODUROARTERIOMYOSYNANGIOSIS: It allows the formation of collateral from STA and deep temporal artery.

iv. OTHER TECHNIQUES: Includes omental transplantation, multiple burr holes, cervical carotid sympathectomy.[30,31,32,33]

5. Combining direct and indirect revascularization :

It has the advantage of immediate revascularization and also revascularization of brain regions outside the distribution of a single major arterial division. Usually, STA-MCA direct bypass is combined with encephaloduralarterysynangiosis. The parietal branch of STA is selected for encephaloduralarterysynangiosis, while frontal for direct bypass. [25]

CONCLUSION

Moyamoya disease (MMD) refers to Cerebrovascular abnormalities with a hazy network of angiographic findings who may have genetic susceptibilities but no associated conditions. The angiographic findings differ according to the stages of MMD. The current diagnosis is based on the presence of basal collaterals.

Cerebral ischemia and Cerebral hemorrhage are the distinctive signs. These signs differ in pediatric and adult populations. Studies have shown that approximately 10% of the population has genetically inherited this disease. Pathophysiology is complex following neovascularization and involvement of progenitor cells and circulating stem cells.

MMD has varying degrees of severity, so not every patient needs surgery immediately. For patients with little to no symptoms, it is often managed with medication to control the contributing risk factors. In case of stroke or

hemorrhage, surgical procedures to improve blood flow to the brain are often recommended. The management differs in the pediatric and adult populations.

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