Review Article

Moyamoya Disease: A Review of Literature

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ABSTRACT

Moyamoya disease is a rare progressive cerebrovascular disorder caused by blocked Supraclinoid Internal Carotid Arteries at the base of the brain in the basal ganglia area. It is a chronic and progressive condition. The word "Moyamoya" is Japanese which refers to a hazy puff of smoke or cloud due to the appearance of blood vessels like a puff of smoke in angiograms of people suffering from this disease. The exact etiology of Moyamoya disease remains unclear, but there seems to be genetic and acquired forms. The first sign of Moyamoya disease is usually stroke or recurrent Transient Ischemic Attacks (TIAs) also called "mini-strokes". Some other symptoms may include brain hemorrhage, headaches, developmental delays, aneurysm, involuntary movements, problems with cognitive abilities, problems with the senses, seizures, hemiparesis, ischaemic stroke or hemorrhagic stroke. Despite the etiology of Moyamoya disease being unclear, there are certain factors which may increase the risk of getting the disease, like Asian ancestry, family history of Moyamoya disease, other medical conditions, being female and being young. Moyamoya disease has a very unclear etiology and pathogenesis. Moyamoya disease can be diagnosed using tests like Cerebral Arteriography, Magnetic Resonance Angiography (MRA), Magnetic Resonance Imaging (MRI), etc. There is no cure for Moyamoya disease, but can be treated using drugs and surgical procedures. Hence, extensive studies need to be conducted in order to better determine the exact pathophysiology of the disease and also to find more effective treatment options that would further improve the prognosis in patients with Moyamoya Disease.

Keywords: Aneurysm, Angiograms, Hemiparesis, Moyamoya, Supraclinoid.

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INTRODUCTION

Moyamoya disease is a rare progressive cerebrovascular disorder caused by blocked Supraclinoid Internal Carotid Arteries at the base of the brain in the basal ganglia area.[1] It is a chronic and progressive condition. This disease is characterized by the narrowing and closing of one or both of the carotid arteries in the basal ganglia region of the brain which leads to blockages, ultimately causing ischemic stroke, seizures and hemorrhagic stroke. It can lead to recurrent brain hemorrhage and strokes in the affected areas of the brain.[2]

The word "Moyamoya" is Japanese which refers to a hazy puff of smoke or cloud due to the appearance of blood vessels like a puff of smoke in angiograms of people suffering from this disease.

Moyamoya disease is different from Moyamoya syndrome, in the sense that, the blood vessels of patients suffering from Moyamoya syndrome have a similar radiographic appearance but the narrowing of the arteries is caused by mechanisms other than genetic mutation, which is the primary cause of Moyamoya disease. There is no cure for Moyamoya disease.

Etiology

The exact etiology of Moyamoya disease remains unclear, but there seems to be genetic and acquired forms.

In some cases, Moyamoya disease may be associated with other conditions, and this is called Moyamoya syndrome or phenomenon. Some of these other conditions include:[3]

1) Down syndrome.
2) Grave's disease.
3) Neurofibromatosis type 1.
4) Sickle cell disease.
5) Atherosclerosis.
6) Radiation vasculopathy.

Symptoms

The first sign of Moyamoya disease is usually stroke or recurrent Transient Ischemic Attacks (TIAs) also called "mini-strokes". Some other symptoms may include:[4]

1) Brain hemorrhage.
2) Headaches.
3) Developmental delays.
4) Aneurysm.

5) Involuntary movements.

6) Problems with cognitive abilities.

7) Problems with the senses.

8) Seizures.

9) Hemiparesis.

10) Ischaemic stroke (due to blockage) or hemorrhagic stroke (due to bleeding).

Risk Factors

Despite the etiology of Moyamoya disease being unclear, there are certain factors which may increase the risk of getting the disease, like:[5]

1) ***Asian Ancestry:*** Moyamoya disease, though found in all parts of the world, is more prevalent in East Asian countries like Japan, Korea and China. This disease has been found to be more prevalent in people with Asian ancestry.

2) ***Family history of Moyamoya disease:*** If a family member is suffering from Moyamoya disease, a person belonging to this family has an increased risk of getting this disease, and this risk is several fold more than the general population. This factor strongly indicates a genetic link with the disease.

3) ***Other Medical Conditions:*** Sometimes Moyamoya syndrome occurs along with other medical conditions like Neurofibromatosis type 1, Sickle cell disease, Down syndrome, etc.

4) ***Being Female:*** Women are at a higher risk of getting Moyamoya disease.

5) ***Being Young:*** While adults can also get Moyamoya disease, children below the age of 15 are more susceptible to this disease.

Pathophysiology

Moyamoya disease has a very unclear etiology and pathogenesis. Studies show a possible link between Moyamoya disease and certain etiological factors like stem cell involvement and genetic factors in the pathophysiology of Moyamoya disease.

Moyamoya disease is characterized by the progressive stenosis and occlusion of bilateral Internal Carotid Arteries with recurring association of both the proximal anterior and middle cerebral arteries. The affected segments of ICA in patients with Moyamoya disease have shown abnormal fibrocellular thickening of the intima or endothelium, proliferated Smooth Muscle Cells (SMCs), distinctly tortuous and often duplicated internal elastic lamina, with no artheromatous or inflammatory involvement. Excessive collection of SMCs and thrombosis within the lumen leads to obstruction in the blood vessels. It is believed that due to arterial stenosis or obstruction, the regions of the brain where hypoxia is observed, the brain stimulates the formation of collateral blood vessels called Moyamoya Collaterals (through the process of collateralization) which are dilated and twisted perforated arteries to compensate for the decreased blood flow to the brain resulting in hypoxia leading to ischaemic strokes.

This revascularization occurs as a result of expression of several growth factors which play an important role in angiogenic signaling cascades, namely HIF-1, VEGF, bFGF, transforming growth factor-β1, hepatocyte growth factor and MMPs. These factors create an intracranial environment which promotes angiogenesis in patients with MMD.[6]

Moyamoya disease has two pathophysiologies:

In the first pathogenesis, the activation of vascular growth factors like VEGF, TGF, HGF, MMPs occurs which leads to fibrocellular thickening of intima. This causes irregular undulation of the internal elastic lamina, attenuation of media and decrease in outer diameter of the affected arteries. This causes the narrowing of Vessel lumen ultimately leading to hypoxia and Transient Ischaemic Attacks (TIAs).

In the second pathogenesis, the activation of vascular growth factors like VEGF, TGF, HGF, MMPs occurs which leads to neovasculogenesis causing “Moyamoay vessels” to form, which results in ischaemic stroke, hypoxia and formation of microaneurysms causing hemorrhagic stroke.[7]

Diagnosis

If Moyamoya disease is suspected, the following tests may be required:[8]

1) ***Cerebral Arteriography:***

A small tube called a catheter is inserted into an artery in the arm or leg. This catheter is then used to inject iodine contrast dye into the bloodstream. X-ray scans are taken of the dye in the blood vessels. This test is used to know how many blood vessels have become narrow and to understand blood flow patterns.

2) ***Magnetic Resonance Angiography (MRA):***

This is a non-invasive diagnostic test which uses a magnetic field, radiowaves and acomputer to assess the inside of blood vessels for any unusual changes.

3) ***Magnetic Resonance Imaging (MRI):***

MRI is similar to MRA, meaning, it uses magnetic field to produce images of the organs, blood vessels, etc., and to understand how the blood flow in the brain looks.

4) ***Transcranial Doppler Ultrasound:***

In this test, sound waves are used to create images of the head and the neck. This test is used to assess the blood flow in the blood vessels in the neck.

5) ***Electroencephalogram (EEG):***

In this test, a series of electrodes are placed on the scalp in order to monitor the electrical activity in the brain.

Children suffering from MMD usually show EEG abnormalities.

6) ***Positron Emission Tomography (PET) scan or Single-Photon Emission Computerized Tomography (SPECT):***

In these tests, a small amount of radioactive material is injected into a vein and emission detectors are placed over the brain. PET scan shows visual images of brain activity and SPECT scan helps to measure the blood flow into different regions of the brain.

7) ***Computerized Tomography (CT) scan:***

In this test, X-rays are used to produce an accurate image of the brain. A dye is injected into a blood vessel which is used to highlight the blood flow in arteries and veins (CT angiogram). This scan may not be precise enough to diagnose early stages of MMD but it can still identify abnormal blood vessels.

Management

There is no cure for Moyamoya disease, but it can be treated. MMD can be treated either medically or surgically.[9] The following are certain medications used to treat Moyamoya disease:

1) ***Aspirin:***

Aspirin is used to prevent blood clots in the smaller, backup blood vessels.

2) ***Anticonvulsants:***

These drugs are used to prevent seizures caused by Moyamoya disease.

3) ***Anticoagulants:***

These drugs work by thinning the blood and are used to prevent blood clots by inhibiting the release of clotting factors, but they may cause severe bleeding that can be difficult to stop. Hence, they are prescribed only in certain cases.

4) ***Calcium Channel Blockers:***

These drugs may be used to reduce headaches caused by Moyamoya disease but can also lead to decrease in the blood pressure, thereby increasing the risk of stroke. Calcium Channel Blockers are used only in few cases.

The medications prescribed for Moyamoya disease cannot prevent the narrowing of the blood vessels, so the disease may keep on worsening.

Surgical Treatment

Moyamoya disease can be surgically treated through cerebral revascularization techniques like direct bypass surgery [STA-MCA anastomosis] or by indirect bypass procedures such as EMS, EDAS, EMAS and Omental transposition.

Direct Bypass Procedure [STA-MCA anastomosis]:

STA-MCA stands for Superficial Temporal Artery- Middle Cerebral Artery. The Superficial Temporal Artery (STA) arises from the External Carotid Artery as a terminal branch.[10] STA-MCA bypass is a type of direct revascularization surgery most often performed in patients with Moyamoya disease or Intracranial Artherosclerotic Disease (ICAD), in which the STA is dissected and passed through a craniotomy and directly attached to a branch of the Middle Cerebral Artery (MCA). STA-MCA anastomosis seems to be an effective treatment of Moyamoya disease.[11]

Indirect bypass procedures:

Indirect bypass procedures like Encephalomyosynangiosis (EMS), Encephaloduroarteriosynangiosis (EDAS) and Encephaloduroarteriomyosynangiosis (EDAMS) are generally preferred in children and considered to be safer as children have smaller blood vessels.

In EDAS, a branch from the STA is directly laid on the brain's surface without performing any direct anastomosis. Once this procedure is completed, the STA will grow new blood vessels into the brain through angiogenesis and increase the blood flow to the previously hypoxic parts of the brain. If an STA is used once for an indirect bypass, it cannot be used again for a direct bypass procedure in the event that the indirect bypass fails. Once this procedure has been completed, it takes a minimum of 3-6 months for angiogenesis to occur and develop new blood supply to the affected part of the brain.

EMS is another type of indirect bypass procedure in which the temporalis muscle found in the temple region of the forehead is dissected. This temporalis muscle is then placed on the brain surface through an opening in the skull. EMS, similar to EDAS, also requires 3-6 months for a new blood supply to form from the transposed muscle.

Omental Transposition

The peritoneum is a large membrane present in the abdominal cavity whose main function is to connect and support the internal organs. It consists of several folds which pass between and around the organs among which there are two very important folds, namely the Omentum and the Mesentery. The Omentum is situated in front of the stomach and the intestine. The Omentum is richly supplied with blood vessels, lymph nodes, nerves, fat, collagen fibres and elastic fibres. The Omentum has a lace-like appearance.[12]

Omental transposition is a novel brain revascularization procedure in which the abdomen is opened and the Omentum is released from the surrounding attachments. This Omentum is then lengthened greatly. This membrane is passed through a subcutaneous tunnel along the chest and neck, to behind the ear, then brought out from under a skin flap and subsequently brought over the surface of the brain through an opening present in the skull. The transposed Omentum produces new blood vessels

through angiogenesis, thereby establishing a new blood supply to the affected parts of the brain. As the Omentum is highly vascularized, it is perfect for re-establishing blood supply to ischaemic areas of the brain, as observed in Moyamoya disease.

Omental transposition has been performed in patients who have previously undergone direct or indirect revascularization procedures which have failed to establish a new blood supply to the ischaemic parts of the brain.[13]

Combined Revascularization Techniques

Surgeons have begun combining direct and indirect revascularization techniques in the recent times, in order to treat Moyamoya disease. For instance, STA-MCA bypass can be combined with EDAMS in order to establish successful revascularization in the affected parts of the brain. The direct bypass procedure focuses on immediate hemodynamic improvement, while the indirect bypass is aimed to improve the outcome of the surgery and to also act as a contingency plan in the event that the direct bypass fails.[14] Hence combined revascularization techniques have been increasingly employed in the surgical treatment of Moyamoya disease.

Other combined procedures like STA-MCA along with EMS have been increasingly preferred in children in instances where the direct bypass has a greater risk of failure and the indirect bypass has a higher success rate.

CONCLUSION

Moyamoya disease is a chronic, idiopathic occlusive cerebrovascular disease involving the major cerebral arteries in the brain. Patients suffering from Moyamoya disease may experience strokes as blood vessels become increasingly narrowed with time and the condition only worsens over time. There is no way to prevent Moyamoya disease which has a genetic etiology. Pharmacological treatment of Moyamoya disease cannot prevent the blood vessels from narrowing, as the condition worsens, but may help with the symptomatic treatment of the disease and can buy some time until a cerebral revascularization surgery can be performed.

The pathophysiology of Moyamoya disease still remains unclear. Diagnosis of MMD should be made at the earliest in order to prevent severe neurological symptoms and also to ensure better prognosis. Revascularization surgery plays an extremely crucial role in the management of MMD and to reduce the rate of ischaemic and hemorrhagic strokes. It is also key in improving neurological and neuropsychological outcomes in MMD patients. Surgically treated patients have better outcomes and seem to be doing well when compared to patients who have been treated with medicines alone.

In conclusion, extensive studies need to be conducted in order to better determine the exact pathophysiology of the disease and also to find more effective treatment options that would further improve the prognosis in patients with Moyamoya Disease.

Abbreviations:

ICA: Internal Carotid Artery

MMD: Moyamoya Disease

SMC: Smooth Muscle Cells

MMP: Matrix Metalloproteinases

STA: Superficial Temporal Artery

EDAS: Encephaloduroarteriomyosynangiosis

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