# LONG TERM OUTCOME OF MOYAMOYA ANGIOPATHY

**Submitted for M.Ch Neurosurgery By**

**Dr. Sam Scaria**

**2019-2023**

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND

TECHNOLOGY, TRIVANDRUM

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A THESIS SUBMITTED BY

**Dr.Sam Scaria**

TO

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM.

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE AWARD OF

Programme: M.Ch Neurosurgery

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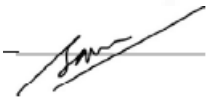
# DECLARATION BY THE STUDENT

## CERTIFICATE

I, Sam Scaria hereby certify that I had personally carried out the work depicted in the thesis titled, “Long term outcome of moyamoya angiopathy.”

No part of this thesis has been submitted for the award of any other degree or diploma prior to this date.

Signature



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Date: 30/7/2023

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The thesis entitled, "Long term outcome of moyamoya angiopathy" was carried out under my direct supervision. No part of the thesis was submitted for the award of any degree or diploma prior to this date.

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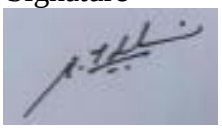

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# APPROVAL OF THE THESIS

The thesis entitled "long term outcome of moyamoya angiopathy"

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Submitted by

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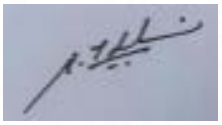

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# LIST OF ABBREVIATIONS

| S No | Abbreviation | Full Form |
|---|---|---|
| 1 | MMA | Moyamoya angiopathy |
| 2 | STA | Superficial temporal artery |
| 3 | MCA | Middle cerebral artery |

If a large number of abbreviations are used in the thesis, which may be unfamiliar to a reader, a list of abbreviations may be useful

# LONG TERM OUTCOME OF MOYAMOYA ANGIOPATHY

SYNOPSIS

BY

**Dr. Sam Scaria**

For MCh Degree of

Neurosurgery

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM

# SYNOPSIS

Background: Surgical management is the standard treatment in moyamoya disease, but there is no clear consensus between outcomes of various types of procedures

Objective: To analyse the immediate and long-term post-operative outcome in patients of moyamoya and to compare the type of procedures

Material and Methods:

Patients with MMD, irrespective of age and type were subjected to surgery. A superficial temporal artery, middle cerebral artery (STA-MCA) anastomosis was attempted in all. It was augmented by an encephalo-duro-myosynangiosis), this was labelled as the combined surgical group. In patients where a direct bypass was not possible encephalo-duro-arterio-myosynangiosis (EDAMS) was performed and were considered in the indirect group. In the followup period the improvement in terms of modified ranklin scale and number of ischemic or haemorrhagic events were noted.

Results:

Seventy five patients underwent 127 surgical revascularization procedures. A combined surgery (STAMCA bypass and EDAMS) was performed in 48 patients and indirect surgery (EDAMS) on 54. In the perioperative period 8 patient developed acute stroke,5 had TIA,3 patients developed seizures. There was no significant difference in the rates of complications between the hemispheres with combined or indirect revascularization (12.5% vs 5 %p-0.2). At 36 months follow-up showed that combined procedure has relatively less number of events than indirect procedure.

Conclusions:

Surgical group with combined revascularization had a better long term event free survival.

Key Words: moyamoya disease, STA-MCA bypass, indirect EDAMS

# INTRODUCTION

Moyamoya angiopathy is characterized by progressive stenosis and occlusion of the supraclinoid internal carotid artery and its branches. The natural course of moyamoya is also devastating, leading to recurring strokes and subsequent neurocognitive decline leading to morbidity and mortality.

The treatments for MMA are limited because no known medical therapy has proven to be effective. Surgical treatment remains the mainstay in the patient management for reducing the future events. The main purposes of surgical interventions are to restore perfusion to oxygen-deprived areas of the brain or indirectly to enable collateral vessel formation. Surgical techniques can be grouped as direct, indirect, or a combined (combination of the two). Most of the clinical studies have been reported from Japan and Korea, there are a few studies from the west and the US also. However the data on moyamoya angiopathy from the Indian population is sparse. Currently the literature does not present a clear consensus regarding the best revascularization technique in the surgical management of MMA. Here we describe our experience of treating of this angiopathy, and compare the clinical outcomes of indirect, and combined revascularization techniques in patients with MMA.

# AIMS AND OBJECTIVES

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This study aims to show experience with revascularization of patients operated over a period of 2007 to 2020. And to study the clinical profile, surgical outcome of patients operated for Moyamoya angiopathy, using various revascularization procedure and to compare the clinical outcome of the procedures; indirect vs combined.

# REVIEW OF LITERATURE

## Introduction

Moyamoya angiopathy is a distinct cerebrovascular condition characterized by chronic, progressive stenotic alteration in the terminal segment of bilateral internal carotid arteries (ICAs).It is frequently seen in East Asian communities, affecting both children and adults, and can cause an ischemic or hemorrhagic stroke, headache, seizures, or a transient ischemic attack. In 1957, Takeuchi and Shimizu described the pathological manifestation of MMA for the first time for bilateral hypoplasia of the ICA. Cerebral angiography in such patients reveals smoke-like blood vessels from ICA in the base of skull, which was officially named Moyamoya angiopathy by Suzuki and Takaku[2]

## Epidemiology

Moyamoya angiopathy is known to be relatively common in Far Eastern countries. Significant regional disparities can be seen in the incidence of MMA, with East Asia having a high incidence and other regions having a low incidence. Moyamoya angiopathy has now been observed throughout the world and redrawn the theory of a singularly Eastern pathology.

According to existing published reports, the incidence of moyamoya angiopathy is high in countries in East Asia, such as Japan, Korea China and Taiwan. In Japan, the annual prevalence and incidence have been estimated at 3·16 and 0·35 per 100,000, respectively[i].MMA affects approximately twice as many females as males in Japan in terms of sex distribution, with a reported female-to-male ratio between 1.8:1 and 2.1:1[ii,iii]. A bimodal age distribution has been reported with the early peak observed in children aged between five and nine years of age, and a second peak adult peak occurring between 45 and 49 years, with ischemia as the most common presenting feature in both the age groups.[5] A familial occurrence between 10% and 15.4% seen across all age ranges, and around 37.8% in the childhood population. Familial MMA also demonstrates a younger mean age of onset. An identical twin study, concordance of angiopathy was observed to be 80%. The female-to-male

ratio in familial MMA is much higher than in the sporadic form at 5.0:1 as opposed to 2.1:1, with a maternal dominance in the inheritance of the angiopathy.

The incidence and prevalence of Chinese MMA are comparable to those of the Japanese populace. For instance, regional epidemiological research in the Nanjing region found that the incidence and prevalence were 0.43 per 100, 000 person-years and 3.92 per 100,000 individuals, respectively[iv].

In the west MMA affects a broad spectrum of individuals, but the exact racial demographics vary according to the region of the selected cohort. In USA Caucasians account for the majority of Patients (35.4–69%), with African-Americans accounting for 19.9–25%, followed by Asian/Pacific Islanders (8.3–10%) and Hispanics (5.6–11%).

The overall incidence of MMA in the USA is much lower than that observed in Asia, with prevalence ranging from between 0.086 and 0.57 per 100,000 person years.[v,8]Data pertaining to MMA in Europe is distinctly lacking but it appears that the phenotype observed in Europe is consistent with that of the USA. The published data from a study of all patients diagnosed with idiopathic MMA between 1996 and 2007 in a German institution demonstrated findings comparable to American

studies. The female to male preponderance was 4.25:1, with no evidence of familial occurrence and had a mean age of angiopathy onset of 31year.

## Clinical Presentation

The clinical presentations of MMA include TIA, ischemic stroke, haemorrhagic stroke, seizures, headache, and cognitive impairment. The incidence of each symptom varies according to the age of the patients.

Moyamoya angiopathy causes cerebral hypo perfusion and ischemia in ICA territories due to progressive major vessel occlusion resulting in repeated hemodynamic TIAs or ischemic strokes. Therefore, most patients with moyamoya angiopathy present with focal neurological signs such as dysarthria, aphasia, or hemiparesis.

It can also present with other atypical symptoms such as syncope, Para paresis, visual symptoms, or involuntary movements, particularly in children.[8,9, 10]

Intellectual impairment owing to frontal lobe ischemia, infarct, or both are seen in infants and children. Rarely adult also can develop cognitive dysfunction, such as short-term memory disturbance, irritability, or agitation; and can be misdiagnosed with psychiatric disorders.[13,14] Adult moyamoya patients commonly presents with

intracranial bleeding. The major causes of intracranial bleeding in moyamoya angiopathy are rupture of dilated, fragile moyamoya vessels and rupture of saccular aneurysms in the circle of Willis or rupture of the dilated collateral arteries on the brain surface.[15]

## Clinical Course of angiopathy and progression

The knowledge on the natural history of MMA is not well studied due to the rarity of the angiopathy in our part of globe. The overall functional outcome assessments and assessment of neurocognitive abnormalities have rarely been recorded, despite multiple research showing that severe neurocognitive deficits parallel the progression of moyamoya phenomena[16]. Despite the wide range of factors affecting reports of the natural history of moyamoya phenomena and its varied course, the angiopathy progresses in most patients and is usually associated with poor outcomes.

The natural history of moyamoya phenomena is difficult to assess and quite variable. Progression may follow several different routes, including intermittent symptom occurrence, latency, slow indolent course, or rapid progression. The rapidity and degree of the arterial blockage, as well as the patient's capacity to establish efficient

collateral circulation, all influence the angiopathy's clinical trajectory. The progression of the angiopathy is often accompanied by the onset of symptoms, with more serious consequences for the patient.

The natural history of rebleeding with haemorrhagic MMA is high and rebleeding is the main cause of mortality in haemorrhagic MMA and hypertension was also found to be associated with mortality.[17]

Asian patients appear to have a more progressive angiopathy phenotype with dynamic radiographic changes and a greater incidence of strokes that continue to occur over time compared to a angiopathy phenotype in Caucasian and African American patients.

Unilateral moyamoya angiopathy is also referred to as probable moyamoya angiopathy and indicates the presence of unilateral stenosis or occlusion of the terminal portion of the ICAs accompanied by the formation of moyamoya vessels.

The diagnosis of asymptomatic cases of moyamoya angiopathy has been increasing with the advent of widespread use of MRI.

The frequency of progression from unilateral to bilateral moyamoya angiopathy has varied from 10 to 39%.A more rapid rate of progression was presumed to be associated with a younger age at

diagnosis. Asymptomatic cases may represent earlier forms of the angiopathy. In a study by Kuroda et al, 20% of patients had a silent infarction and 40% demonstrated impaired vascular hemodynamics on acetazolamide challenge. During a mean follow-up of 43.7 months, 7 of 34 patients who did not receive surgery suffered a TIA, stroke, or intracranial haemorrhage. This showed that the risk of asymptomatic patients becoming symptomatic was 3.2%.

**Pathology:**

The detailed mechanisms through which MMA occurs and progresses remain unknown. Moyamoya angiopathy is characterized by intimal thickening in the walls of the terminal portions of the internal carotid vessels. Various studies reveal that the pathogenesis of MMA may involve angiogenesis, genetic issues, and immunological inflammation.

The recently proposed mechanobiological theory gives an explanation of MMA . In Moyamoya, a phenomena of collateral blood supply formation, emerges after obstruction of major intracranial vessels like the distal ICA and possibly BA in order to give alternate pathways for blood supply to the brain. Combinations of genetic, developmental, hemodynamic, rheological, immunological, biochemical and structural mechanobiological variables lead to the blockage of the major

blood arteries[22].

Researchers found less tube formation and increased senescent-like phenotype when analysing circulating ECFCs in the peripheral blood of children with MMA, suggesting that circulating ECFCs may be associated with MMA pathogenic processes.[23]

Mitochondria of ECFCs from MMA patients exhibited morphological and functional abnormalities as compared with those from healthy individuals. This finding suggests that the mitochondrial abnormalities may have a role in the pathogenesis of MMA. Vascular endothelial growth factor (VEGF), with a relative molecular weight of 45KD, is the only growth factor that has been proven to be specific and critical for blood vessel formation. Overexpression of VEGF could also be found in the endocranium in patients with MMA. Some studies demonstrated that both plasma and dural VEGF levels were significantly elevated in MMA patients than those in normal controls, suggesting an important role of VEGF in angiogenesis.

Based on the existence of familial cases and the observation of a strong ethnicity effect of MMA, a genetic contribution is strongly suspected. It has been demonstrated that several human leukocyte antigen (HLA) alleles are closely correlated with MMA the ring

finger protein 213 (RNF213) on 17q25.3, predominantly expressed in blood cells and the spleen, has been considered to be a novel susceptibility gene for MMA in East Asian populations.[24]
Based on the observation from immunohistochemical staining, infiltrations of T cells and macrophages were discovered in the intima of narrowed and thickened vessels in patients with MMA . Abnormal IgG deposition was also observed in the inner elastic layers of ICA and middle cerebral artery (MCA), implying that immune cell infiltration and immune complex injury shared a certain relationship with MMA, the occurrence of which might be related to the bending, deformation, and destruction of the inner elastic layer .

Furthermore, this immunological process could promote the infiltration of S100A4 positive SMCs into the intima, whereby leading to the formation of typical intracranial vascular stenosis.

Development of MMA is often noted with micro thrombi in the stenotic vasculature. Micro thrombi could cause endothelial injury leading to a thickened intima and smooth muscle cell proliferation as observed in the vessels of MMA cases.[25]Histopathologically, the intima of the major arteries shows eccentrically laminated thickening. This thickness is 2 or 3 times

that of normal vessels and has a wavy appearance representing the discontinuity of the elastic lamina.[26] These changes in the vessel may predispose to micro aneurysmal formation. The frequency of aneurysms in the vertebra basilar system in MMA is much higher than that of the general population. Three types of aneurysms have been described in patients with MMA.

Major artery aneurysms are those that develop from the circle of Willis. These aneurysms are commonly found in the arterial complex of the anterior communicating artery-ACA in patients with unilateral MMA and in the basilar artery in patients with bilateral MMA. Histopathologically, the aneurysmal wall consists of endothelium with adventitial layers and a disappearance of internal elastic lamina and media, which is the same as those found in saccular aneurysms.[32]

Peripheral artery aneurysms, the second type, are responsible for parenchymatous haemorrhage.[33] Two types of aneurysms have been reported—saccular aneurysms and pseudo aneurysms, which consist of fibrin and erythrocytes. The third type,[34] is rupture of dilated moyamoya vessels or dilated collateral arteries on the brain surface.

## Genetics

The greatest evidence for a genetic component to the genesis of this angiopathy is the varying incidence of moyamoya angiopathy between ethnic groups and recognized familial instances. The first genome wide association study on MMA discovered a relationship with RNF213, also known as mysterin and encoding the 591-kDa protein "ring finger protein 213," In 2011.Mineharu et al[28] observed all forms of transmission between generations in their research of Japanese families, and the mode of inheritance of familial MMA was reported to be autosomal dominant with incomplete penetrance with an increased rate of maternal transmission.[27]

Nomura et al [29] observed clinical characteristics (recurrent stroke after first revascularization and final modified Rankin Scale) in Japanese patients over an extended length of time following direct or combined revascularization; they found no statistically significant differences between genotypes. The study confirmed that the p.R4810K variant of RNF213 influences the phenotype at onset, but there were no significant differences between the genotypes after revascularization.

According to Wang et al.[30], both the homozygous and heterozygous p.R4810K variations were linked to early age at

onset in Chinese patients, although there was no discernible difference between patients having the RNF213 p.R4810K variant and non-carriers in the severity of the initial symptoms.

## Associations of MMA

| Congenital Disorders | Acquired Disorders |
|---|---|
| ***Hematological disorders*** | ***Neoplasm*** |
| Anaplastic anemia | Parasellar tumor |
| Fanconi anemia | ***Infectious diseases*** |
| Sickle cell anemia | Leptospirosis |
| Thalassemia | Tuberculosis |
| Spherocytosis | Meningitis |
| Protein C,S deficiency | ***Vascular disorders*** |
| ***Congenital Diseases*** | Cerebral aneurysm |
| Down syndrome | Arteriovenous malformation |
| Neurofibromatosis-I | Venous angioma |
| Tuberous sclerosis | Cavernous angioma |
| Marfan syndrome | Atherosclerotic disease |
| Fibromuscular dysplasia | Renovascular hypertension |
| Osteogenesis imperfect | ***Others*** |
| Turner syndrome | Traumatic brain injury |
| ***Metabolic disorders*** | Cranial irradiation |
| Hyperlipoproteinemia | Oral contraceptive |
| Glycogen storage disease | |
| NADH-CoQ reductase activity | |
| Pyruvate kinase deficiency | |
| Homocystinuria | |

Table 1: Associations of MMA

## Evaluation and Diagnosis

Based on distinctive radiographic features, such as constriction of the ICA's terminal segments and frequently the formation of collateral arteries, moyamoya is diagnosed. Any patient, especially those in the paediatric age range who present with clinical signs suggestive of stroke or TIA, should be evaluated for moyamoya syndrome.

Cerebral angiography is the gold standard investigation[19]. As proposed by a Japanese research committee in 1997, definitive diagnosis of MMA requires the following on cerebral angiography: (1) occlusion at terminal ICA or proximal ACA/MCA, (2) abnormal network of vessels in proximity to the stenosed vessel, and (3) bilateral involvement.

It has been proposed that MRA be utilized as the primary diagnostic imaging modality for Moyamoya syndrome instead of conventional cerebral angiography due to the good diagnostic yield and non-invasive nature of MRI.

In 2012, revisions were made to include MRA findings in the definitive diagnosis criteria. Cases with unilateral involvement were categorized as probable MMA. MRA staging includes the following: (i) occlusion at terminal ICA or proximal ACA/MCA. (ii) presence of abnormal vessels in the basal ganglion, which can

also be diagnosed by multiple flow voids on MRI of the brain and (iii) bilateral angiography findings.[20]

A magnetic resonance imaging (MRI) or computerized tomography (CT) of the brain is often the first test performed on a patient in the case of suspected Moyamoya syndrome. Small patches of hypo density suggestive of stroke are frequently seen on CT in the periventricular, deep white matter, basal ganglia, and cortical watershed zones.

Patients with these findings on CT are often subsequently evaluated with MRI/magnetic resonance angiography (MRA). MRI shows nonspecific signs like “ivy sign” and “brush sign” . Ivy sign is characterized by diffuse leptomeningeal enhancement, as seen on fluid-attenuated inversion-recovery (FLAIR) or contrast-enhanced magnetic resonance images . Brush sign is characterized by the increased visibility of deep medullary veins, seen best on susceptibility-weighted MRI.

Although MRA can identify stenosis in the major cerebral arteries, artefact frequently interferes with the detection of basal Moyamoya collateral vessels and smaller vascular occlusions. Therefore, conventional cerebral angiography is often needed to establish the diagnosis of Moyamoya syndrome as well as to see

the morphology of the affected arteries and the patterns of flow through the hemispheres.

Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (CBF-SPECT) have both been successfully used to assess cerebral blood flow (CBF), which has significant implications for the diagnosis and staging of the severity of cerebral ischemia/infarct in MMA (ischemic type). Low CBF is also an indication that revascularization surgery is necessary.

Trans cranial Doppler (TCD) is an adjunctive method for monitoring cerebral hemodynamics and data of its ability to determine the stage and/or treatment method is scarce. Additionally, it is operator dependent, hence, it is not as useful as MRI, MRA or conventional angiography. Major parameters of monitoring using TCD are mean blood flow velocity and the pulsatility index.[21]

Another adjunct that could be used is electroencephalography (EEG); EEG evaluations are necessary for patients presenting with seizures. High-voltage slow waves on EEG develop after the end of hyperventilation in children with MMA who present with cerebral ischemia. This is also known as the “rebuild-up”

phenomenon.

Suzuki and Kodoma mentioned the distinctive EEG finding among 50% of moyamoya patients, known as the 'Rebuild-up' phenomenon.[50] The rebuild-up phenomenon is referred to as a reappearance of slow waves of higher amplitude (normally seen during hyperventilation), within 20-60 seconds following termination of hyperventilation which is not seen in any other pathology. Rebuild-up is different than initial slowing due to hyperventilation and signifies the diminished blood flow. Slowing due to rebuild-up is resolved in approximately 10 minutes.

In 2021 Research Committee on Moyamoya Disease and Japan Stroke Society updated new guidelines for the diagnosis of MMA.

Diagnostic Criteria 2021

A. Radiological Findings

Radiological examination such as cerebral angiography is essentially mandatory for diagnosis, the following findings must be present.

In the case of unilateral lesions or lesions complicated by atherosclerosis, it is essential to perform cerebral angiography to exclude other diseases.

1. Cerebral angiography
    a. Stenosis or occlusion in the arteries centered on the terminal portion of the intracranial internal carotid artery.
    b. Moyamoya vessels (abnormal vascular networks) in the vicinity of the occlusive or stenotic lesions in the arterial phase.Both bilateral and unilateral cases can be diagnosed as moyamoya disease.
2. MRI and MRA

Moyamoya disease can be diagnosed when all of the following findings are found on MRI and MRA (time-of-flight; TOF) using a scanner with a static magnetic field strength of 1.5 Tesla (T) or higher

    i. Stenosis or occlusion of the terminal portion of the intracranial internal carotid artery.
    ii. Decrease in the outer diameter of the terminal portion of the internal carotid artery and the horizontal portion of the middle cerebral artery bilaterally on heavy T2-weighted MRI.
    iii. Abnormal vascular networks in the basal ganglia and/or periventricular white matter on MRA.

Moyamoya disease is a disease of unknown etiology, and similar cerebrovascular lesions associated should be excluded as moyamoya syndrome.

## Angiographic classification

**Suzuki stages of moyamoya angiopathy.**

**Stage 1:** 'Narrowing of carotid fork'. On the angiographic exam, only the terminal portion of the internal carotid artery is stenosed.

**Stage 2:** 'Initiation and appearance of basal moyamoya'. On the angiographic exam, stenosis of all the terminal branches of ICA (ACA and/or MCA) and deep moyamoya vessels are seen.

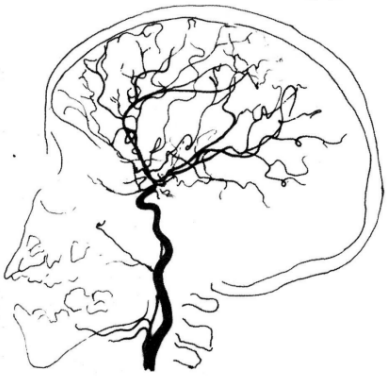
**Stage 3:** 'Intensification of basal moyamoya'. On the angiographic exam, deep moyamoya vessels are intensified. MRA taken during this stage shows a "puff of smoke" appearance. The deflection of the anterior cerebral artery (ACA) and middle cerebral arteries (MCA) is noted.

**Stage 4:** 'Minimization of basal moyamoya'. On the angiographic exam, deep moyamoya vessels begin to regress while transdural collaterals begin to appear. The deflection of the posterior cerebral artery (PCA) is noted.

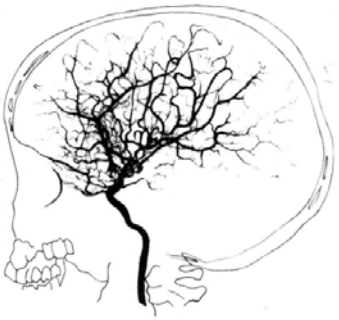
**Stage 5:** 'Reduction of moyamoya'. On the angiographic exam, continued regression of deep moyamoya vessels and progression of transdural collateral vessels are noted.

**Stage 6:** 'Disappearance of moyamoya'. On the angiographic exam, deep moyamoya vessels have vanished and there is complete occlusion of the ICA. Blood supply to ACA and MCA areas is derived mainly from the external carotid artery

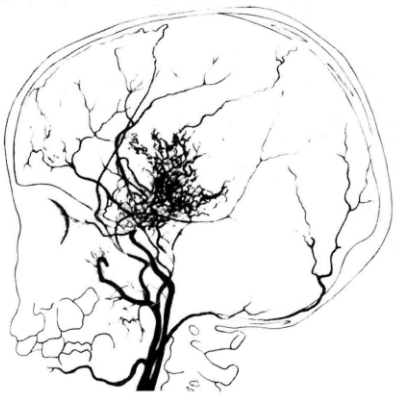
Figure 1: Diagrammatic representation of stages of MMA (Adapted From Jiro Suzuki, M.D., And Namio Kodama, M.D, Stroke Vol 14, No 1, 1983)



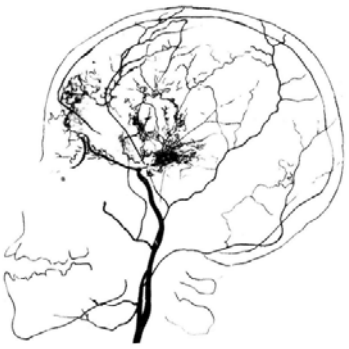
Stage 1. Narrowing of carotid fork. Only the carotid fork stenosis is observed



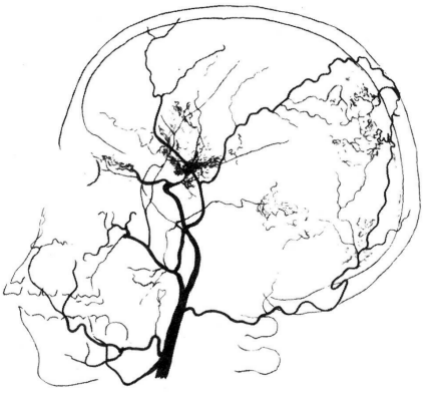
Stage 2. Initiation of basal moyamoya. All the main cerebral arteries are dilated

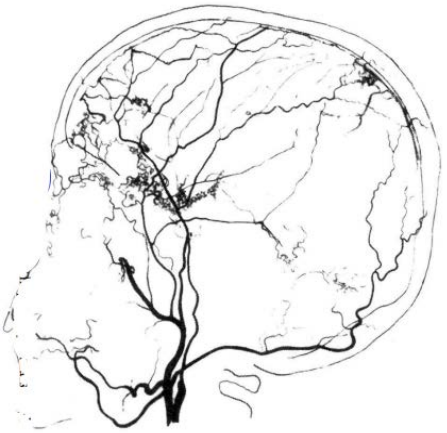


Stage 3. Intensification of moyamoya. Remarkable moyamoya vessels at the base of the brain. The defection of the middle and anterior cerebral arteries is observed



Stage 4. Minimization of Moyamoya. The defection of the posterior cerebral artery is observed.





Stage 5. Reduction ofmoyamoya. All the main cerebral arteries missing.

Stage 6. Disappearance of moyamoya. Cerebral blood flow supplied only from external carotid artery.

Fig 1.1

Diagrammatic representation of stages of MMA

Angiographic representation Suzuki stages

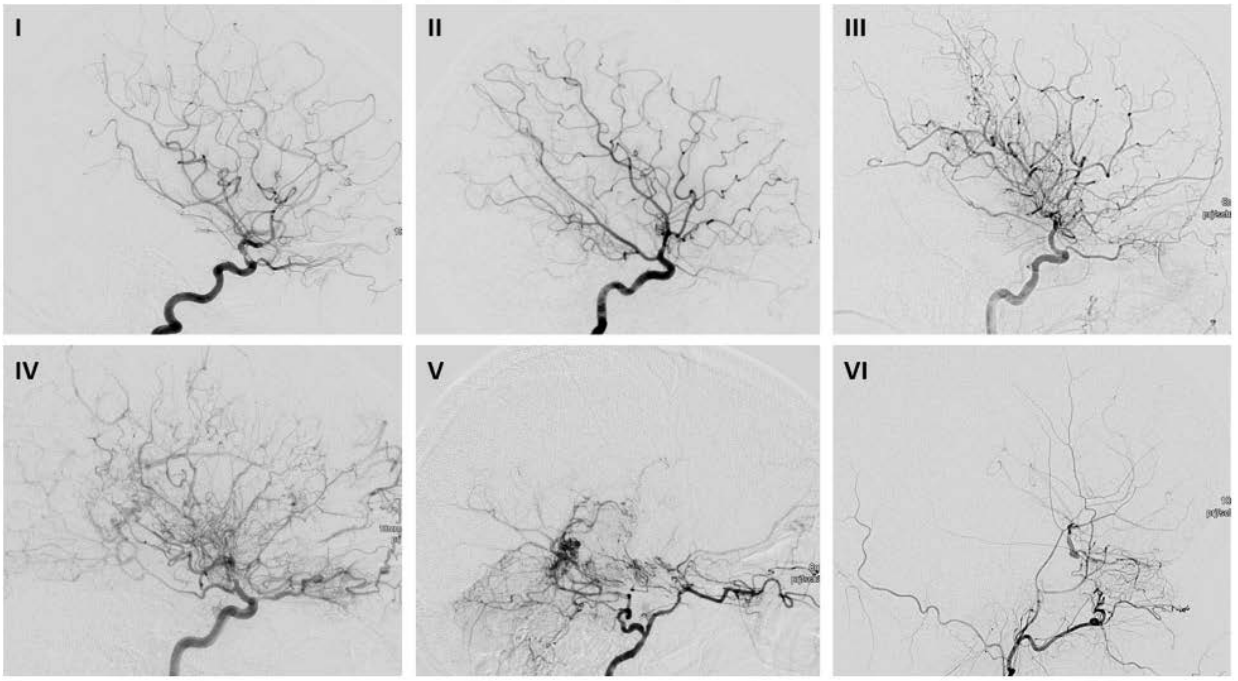



Figure 2: DSA images with lateral views of patients with MMD

(Adapted from The angiographic presentation of European Moyamoya angiopathy. *J Neurol* **269**, 997–1006 )

Fig 1.2

Angiographic representation Suzuki stages

## Management

As medicinal interventions only serve as secondary prophylaxis and do not halt the progression of the angiopathy, early identification of moyamoya angiopathy and prompt surgical surgery are essential. Both medicinal and surgical interventions aim to increase cerebral blood flow. Strokes and/or cerebral haemorrhage are treated acutely according to established methods.

### Conservative management/ Medical therapy

Patients with moyamoya angiopathy have traditionally used aspirin in order to prevent more strokes. However, there is no proof that using antiplatelet medication would help prevent strokes because MMA does not cause endothelial damage, which would cause platelet adhesion. To counteract the risk of subsequent strokes in light of other risk factors and as a maintenance medication to avoid thrombosis and thromboembolism from the stenosed portion of veins after surgical revascularization, aspirin is nevertheless used by many neurologists throughout the world.[54] It is recommended to take the typical dose of 50–100 mg. Analgesics and antiepileptic drugs are typically used to treat the symptoms of headaches and seizures, respectively.

The medical treatment of MMA is roughly classified into treatment for the acute phase of stroke, treatment for preventing recurrence in the chronic phase of stroke, and treatment of asymptomatic MMA.

i. Ischemic MMA The intravenous administration of recombinant tissue-type plasminogen activator (rt-PA) therapy should be carefully considered in the hyper acute phase of ischemic onset MMA. Maintenance of normocapnia should be indicated when mechanical ventilatory support is necessary. Regarding blood pressure control, as in the treatment of other cerebral infarctions, the blood pressure should not be reduced during the acute phase. i. Haemorrhagic MMA In patients with haemorrhagic MMA, antihypertensive therapy can be considered on the basis of the treatment of hypertensive intracranial haemorrhage. Cerebral ischemic attack due to hypotension is of concern during antihypertensive therapy, although there is no evidence.

ii. Prevention of recurrent stroke in the chronic stage involves considering surgical options for patients with ischemic moyamoya angiopathy (MMA). However, long-term

administration of antiplatelet drugs carries a risk of haemorrhagic transformation, so regular follow-up with T2*-weighted imaging to detect micro bleeds may help predict future haemorrhage. Aspirin is the initial treatment of choice, but if it is not effective, clopidogrel or cilostazol can be considered. The safety of clopidogrel has been validated for paediatric patients. However, long-term use of multiple antiplatelet agents increases the risk of haemorrhagic complications, especially in patients with brain atrophy or extensive development of fragile moyamoya vessels.

iii. Medical management of asymptomatic MMA

Asymptomatic MMA patients also have a risk of cerebrovascular events during follow-up. Management strategies aimed at addressing risk factors and guiding lifestyle choices should be applied for the prevention of stroke recurrence in symptomatic MMA patients. However, when considering the use of antiplatelet agents in adult MMA patients, caution is necessary due to the potential risk of a haemorrhagic event.

**Management of Haemorrhagic MMA**

Revascularization surgery is reasonable for haemorrhagic MMA, to prevent recurrent haemorrhage. n the acute phase following intracranial haemorrhage, it may be appropriate to use medication and/or intraventricular drainage to control blood pressure and intracranial pressure, while also considering the potential risk of cerebral ischemia in MMA.[52] Bleeding may occur due to the disruption of dilated collateral vessels or rupture of peripheral aneurysms on these vessels, caused by hemodynamic stress. Revascularization surgery is deemed effective in reducing the recurrence of haemorrhages, as confirmed by postoperative angiography showing a regression of collateral vessels and peripheral aneurysms following the surgery.[53]

## Surgical procedures

This is the only main treatment for MMA with deteriorating cerebral hemodynamics to improve the cerebral blood flow and prevent further strokes.

Evident cerebral ischemia, decreased regional cerebral blood flow, and decreased cerebral vascular reserve in perfusion investigations are the primary reasons for surgical revascularization. However, each case is assessed separately because the deciding elements may differ from one situation to another. Surgery is more beneficial for children since the pediatric form of MMA is usually rapidly progressive.

Indirect revascularization:

This is an easier method to perform but the time to improve the cerebral blood flow is longer than the direct revascularization. Major techniques used under this method are encephalomyo synangiosis (EMS) where the supply comes from the deep temporal artery and encephalo-duro-arterio synangiosis (EDAS) with the supply comes from superficial temporal artery. Encephalo-myo-arterio synangiosis (EMAS), encephalo-duro-arterio-myo synangiosis (EDAMS) and encephalo-galeo

synangiosis (EGS) are variants of EMS and EDAS[52]. The occipital artery can be used as an indirect bypass in case of MMA involving posterior circulation.

Encephalo-myo-synangiosis (EMS) was developed by karasawa and colleagues,Involves direct placement of the temporalis muscle on the cerebral cortex. The clinical and experimental basis for using EMS in Moyamoya was based on the reports of Henschen and Tsubokawa et al.

Encephalo-arterio-synangiosis (EAS)

It was developed by Touho .EAS is mainly an intermediate procedure most often used as part of an EDAS or EDAMS.[52] It, however, has been described as a single procedure in the past when a direct anastomosis between the STA and the MCA cannot be achieved due to MCA insufficiency.

Encephalo-myo-arterio-synangiosis (EMAS)

The temporalis muscle flap with the STA branch attached is sutured to the dural edge to make contact with the frontal cortical surface. This technique can be applied to posterior and middle

cerebral circulation as well using the posterior branch of the superficial temporal artery and the posterior auricular or the occipital artery as needed.

Encephalo-duro-arterio-synangiosis (EDAS)

Matsushima and colleagues developed EDAS[52] with the assumption that the operation would cause the formation of spontaneous anastomoses between the arteries of the cerebral cortex, dura mater and scalp to treat Moyamoya angiopathy. The STA is mobilised and placed directly on the cortex. The free artery with a cuff of surrounding soft tissue is simply sutured to the dura. there are many variants and adjuncts put onto the technique by individual surgeons for additional support for revascularization.

Encephalo-duro-galeo (periosteal)-synangiosis (EDGS)

It incorporates multiple incisions and has been shown to be beneficial mainly for ACA territory ischemia by Kawamoto and colleagues and is used as an adjunct with EDAMS.

Encephaloduroarteriomyosynangiosis

EDAMS is an extended technique from the EDAS and the EMS that uses the temporalis muscle's deep temporal artery, the STA, and the Middle meningeal artery (MMA) to act as adjuncts to facilitate neovascularization. It was proposed and developed in 1984 by Kinugasa and colleagues[52].After reflecting the skin flap anteriorly, both branches of the STA with attached strip of galea are carefully dissected from the pericranium and the fascia. A mini craniotomy is made in the fronto-parietal temporal region while protecting the middle meningeal artery and other dural vessels as well as the dissected STA branches. The dura is opened in both the frontal and temporo–parietal regions alongside the MMA, creating two flaps with the MMA. The temporalis muscle is sutured on to the opened dura at cortical surface.

**Direct Revascularization**

Surgical treatment of MMA goes back to 1970s, when first direct revascularization via an anastomosis of the superficial temporal artery to middle cerebral artery (STA-MCA bypass) was introduced for children and adult patients with MMA

Since then, STA-MCA bypass has been the most common direct revascularization procedure that mainly addresses the MCA territory but also supports the anterior cerebral artery (ACA) territory via leptomeningeal anastomoses. There are further direct bypass methods available, such as STA-ACA, STA-PCA, and occipital artery-PCA anastomosis, if necessary, to particularly address ACA or posterior cerebral artery (PCA) areas.[52]

Large caliber grafts could also be used as a backup plan if STA is not an option or if the STA-MCA bypass fails. For high-flow bypass or intermediate-flow bypass, radial artery or saphenous vein grafts have been employed in the past.

However, because of a possible danger of reperfusion haemorrhage, their usage is currently being debated.

**Combined procedure**

Through an incision between the parietal eminence and the zygomatic process, the Superficial Temporal Artery (STA) is severed and separated during the surgical procedures.[50]

A plane is created in the soft tissue layers of scalp beneath the galea and skin flaps are raised. The frontal and parietal branches of STA are dissected and prepared for anastomosis if sufficient calibre is there.

The STA is divided and mobilised along with a cuff of of tissue and kept moistened during the procedure. Then, by making a subperiosteal plane, the temporalis muscle is separated from the temporal bone and a tunnel is created within the muscle for the STA .Minicraniotomy is done and dura is separated with preserving the MMA. The dural flaps are elevated, protecting the main meningeal artery and its branches .The vault surface of the dura is made to comes into direct contact with the brain, and is tucked inside.

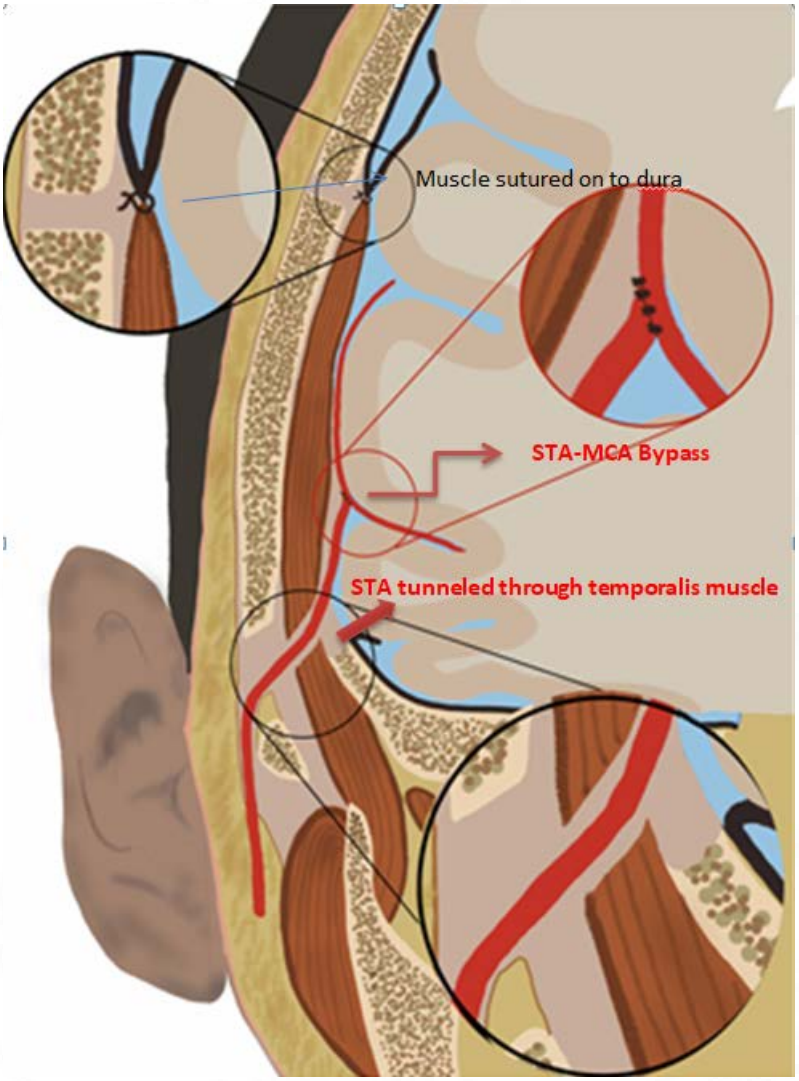



Figure 3 Combined procedure diagram *(Adapted illustration of combined procedure from sudhirBJ et al* Neurosurg Focus. 2021 Sep;51*)*

Intraoperative views

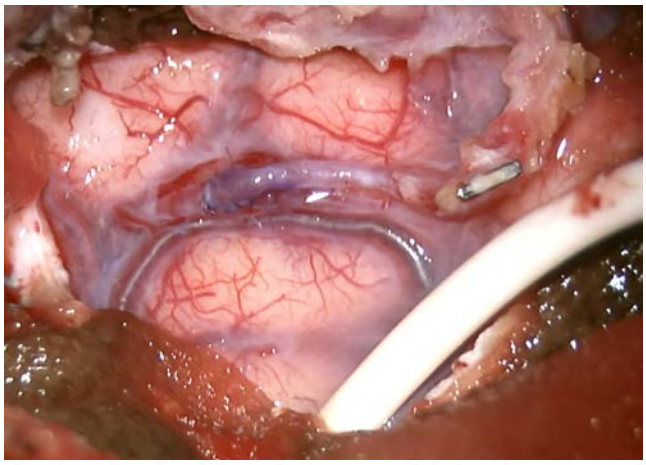


Fig 4.1 Intraoperative views
(a) STA MCA bypass

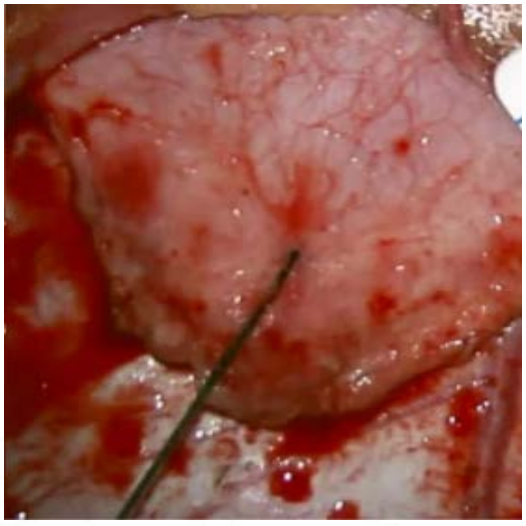


Fig 4.2 Intraoperative views b
Temporalis muscle
attached with Dura

*(b )Temporalis muscle attached with dura*

# MATERIALS AND METHODOLOGY

After obtaining clearance from the Institute Ethics Committee medical records of patients with a diagnosis of moyamoya angiopathy or moyamoya syndrome, treated at our hospital between 2007 and 2020 were reviewed.

a. Clinical data

Patients with angiographically confirmed MMA, who underwent a surgical revascularization procedure, were included in the study, irrespective of age. The data of all patients with MMA were analysed for demographic and clinical profile. Patients with moyamoya syndrome associated with conditions like Down syndrome, neurofibromatosis and unilateral moyamoya cases were also included. Preoperative and post-operative events were compared in patients who underwent revascularisation procedures. The clinical outcome was analysed based on the modified Rankin score, and number of postoperative clinical events. The clinical outcome and stroke events were analysed based on the records obtained from the most recent outpatient visits and imaging studies. Preoperative clinical and radiological parameters were analysed for

predictors of perioperative and postoperative, long-term outcomes after surgical revascularization.

Radiological parameters studied include the pattern and type of infarcts, vascular territory, volume loss and presence of ivy sign from Magnetic Resonance Imaging (MRI) and degree of stenosis of internal carotid artery (ICA), middle cerebral artery (MCA) and anterior cerebral artery (ACA) from angiograms were determined and classified according to Suzuki staging in each hemisphere. Preoperative and post-operative events were classified as minor or major events. Minor events included TIA, focal seizure, or new clinically silent infarctions or haemorrhages picked up on imaging, while major events included strokes with neurological deficits lasting more than 24 hours, symptomatic major vascular territorial or watershed area ischemic stroke and haemorrhagic stroke. Those events that occurred within 4 weeks after revascularisation surgery were defined as perioperative events.

The primary end points in the study were the incidence of recurrent TIA or stroke or death in the follow up period. Modified Rankin scale (mRS) was used for assessing functional outcome, as it allowed patients to be classified according to their functional status and helps in comparing the outcome based on surgical interventions

and effects of postoperative complications. The score ranges from 0 to 6 and lower values indicates a good functional outcome. The patients were clinically assessed during the pre-operative evaluation sessions, and post-operatively, at regular intervals of 3 months, 6 months, and yearly thereafter.

b. Surgical procedure

The surgical strategies were individualized for each patient after a combined discussion between neurologist, neuroradiologist and neurosurgeon. Surgical procedures are classified as combined procedures (superficial temporal artery to middle cerebral artery bypass with encephaloduromyo synangiosis) and indirect bypass procedures (encephaloduroarteriomyosynangiosis: EDAMS or combinations thereof). The symptomatic hemisphere is considered for revascularization first followed by the other side. The decision on the side of initial surgery and the type of surgery was also influenced by the extent of post-infarct cerebral atrophy. Surgical revascularization was deferred in acute phase of cerebral infarctions and was considered only after a minimum of 6 weeks. In cases where an event free interval was not attained, only indirect procedure was performed.

A post-operative CT scan was done to rule out surgical complications and hyper-perfusion injury. Aspirin was stopped for one week prior to the surgery and restarted in the post-operative period.

Flowchart of patient groups, with age (at first event), distribution and surgical procedures done in different groups

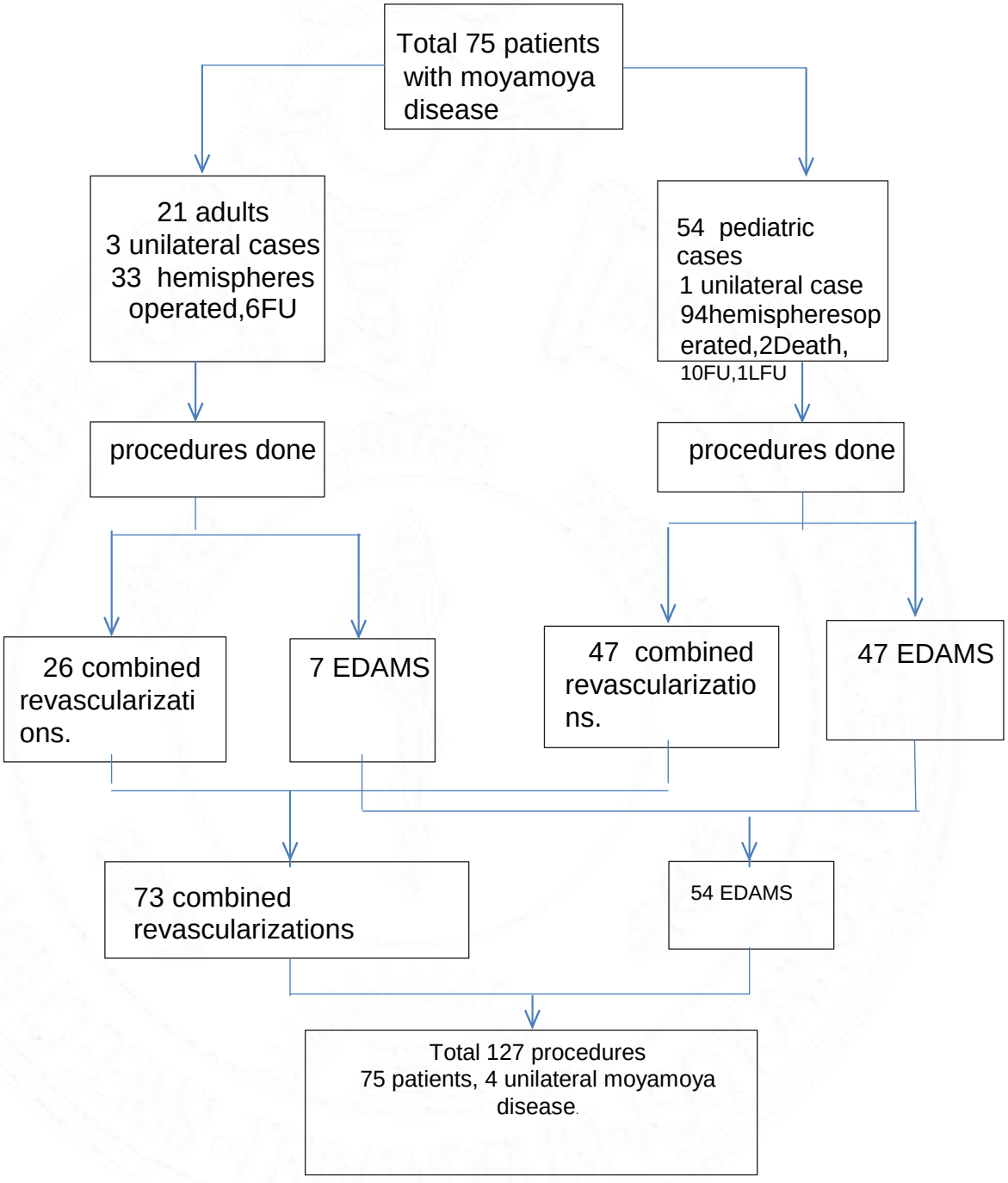



Fig 5.Flow chart showing procedures in patients

# RESULTS

## Demographic and Clinical presentation

A total of 75 patients with a diagnosis of MMA, underwent surgical revascularization surgeries on 127 hemispheres. The mean follow-up duration was 45 months (range 5 to116months). Moyamoya angiopathy was diagnosed in 66 (88 %) of the 75 patients, 4(5.3%) had unilateral moyamoya angiopathy and moyamoya syndrome was diagnosed in 9 (12%).

There were 21 males and 54 females in the cohort. In paediatric group there were 11 males and 41 females whereas in adult group there were 10males and 13 females. The mean age at onset of symptoms for the paediatric patients was 30.3 years and 4.8 years for adults.

The overall female to male ratio was 2.5:1, and a female preponderance was also noted in the paediatric subgroup; 3.7:1.

The mean age at presentation was 14.9 years, (range 0.5 to 51.5 years). The age distribution showed a bimodal pattern with

paediatric peak at 5 years and adult peak at 35 years.

The time interval between initial event and surgical intervention was 21.97 + 30 months, and median is 10.3 months. The mean age at symptom onset was 12.5 years. One patient had a family history of MMA.

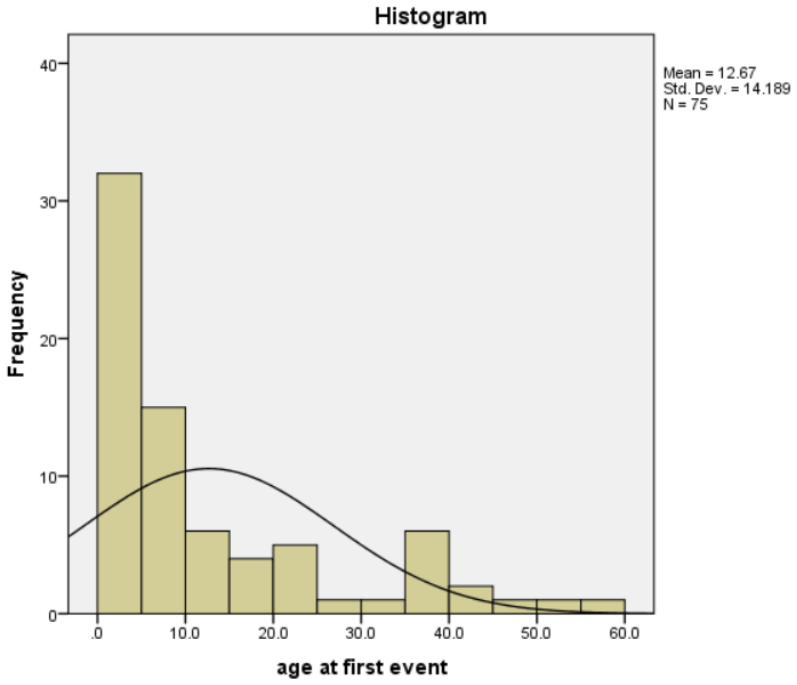



Fig 5.1 Histogram age distribution

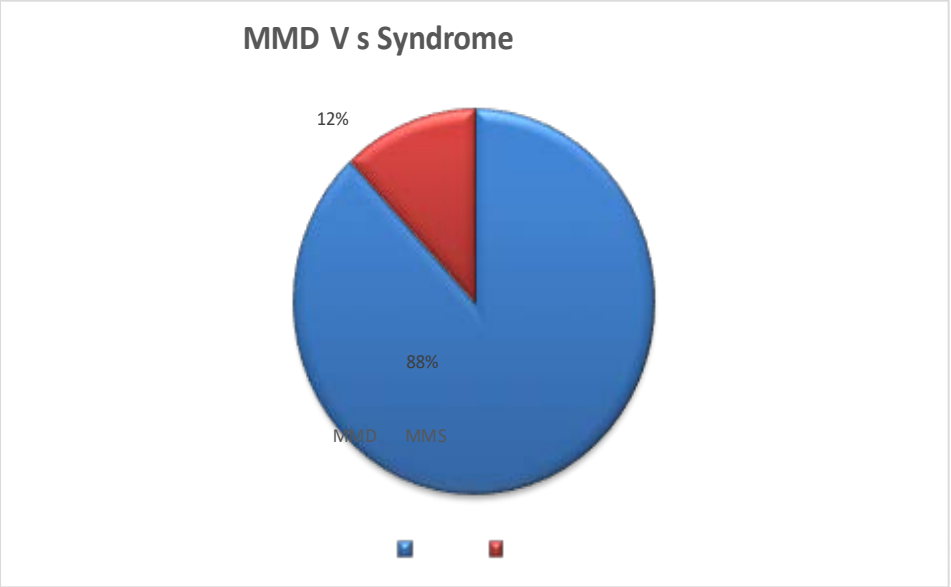



Fig 5.2 MMD V s Syndrome

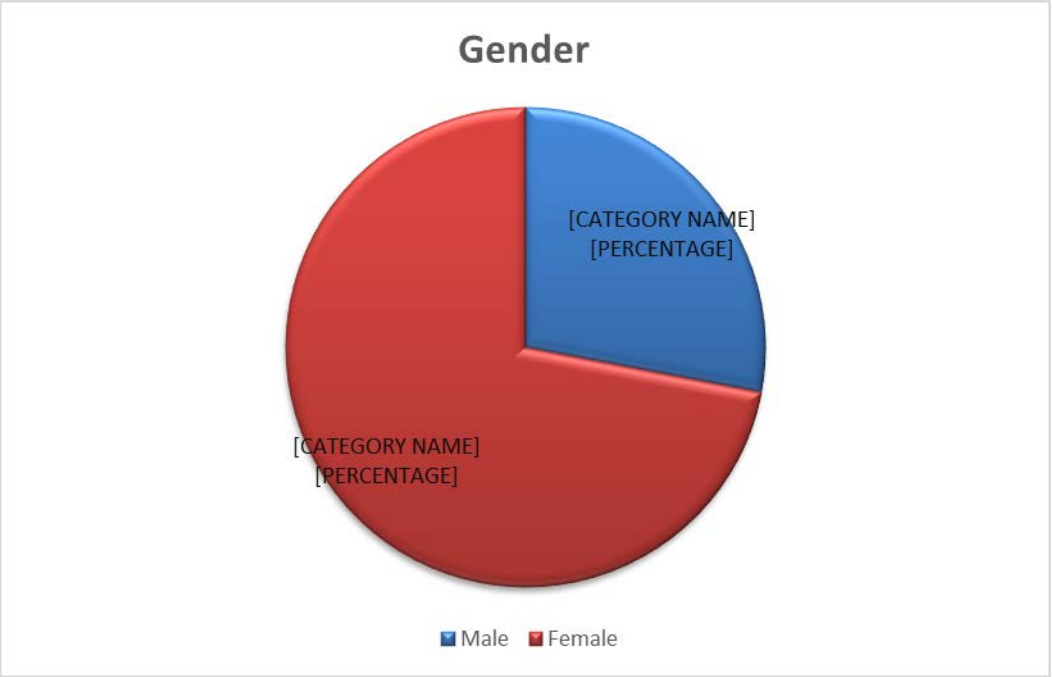



Fig 5.3
Gender distribution

Majority of the patients in our cohort (92%) presented with ischemic events. A presentation with intracerebral hemorrhage was seen in only in adults and constituted 8%. One patient had both ischemic and hemorrhagic manifestation. Of the 75 patients, 45.3% had unilateral symptoms, whereas 54.7% had bilateral symptoms. Hypertension was present in 13% of patients.

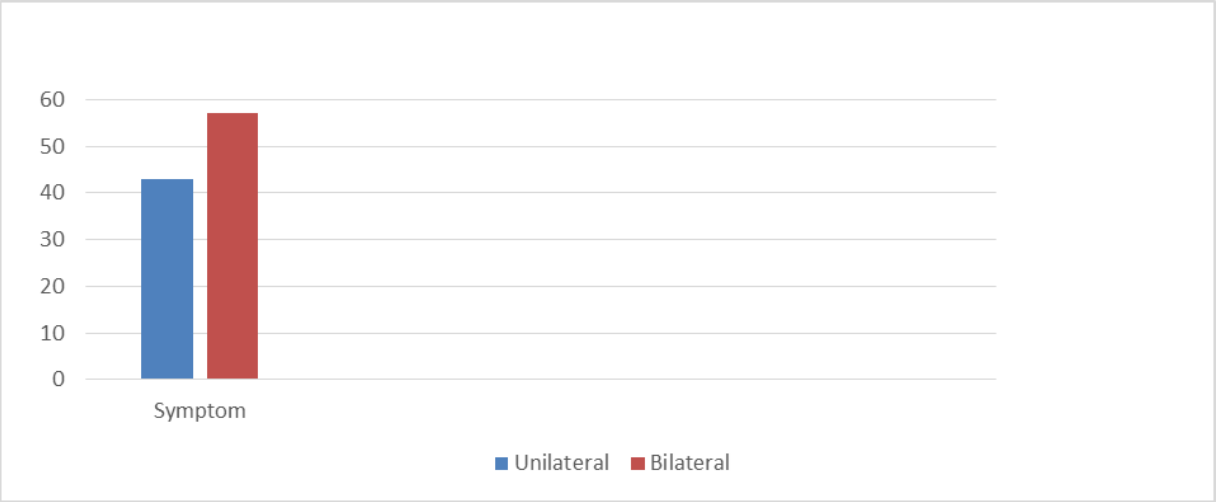



Fig 5.4 Types of presentation

## Clinical and demographic pattern

| Demographic Characteristics | All | >18y | <18 |
|---|---|---|---|
| Total number | 75 | 21 | 54 |
| MMS | 9 | 0 | 9 |
| MMA | 66 | 23 | 43 |
| Gender ratio | 2.5:1 | 1.1:1 | 3.9:1 |
| Age at presentation,(mean in years) | 12.5 | 31.9 | 4.9 |

Table 2.1
Demographic Characteristics

| Presenting symptoms ( %) | | | |
|---|---|---|---|
| Stroke | 68 | 69.35 | 67.3 |
| TIA | 43.2 | 45 | 42.6 |
| Headache | 17.3 | 19 | 16.7 |
| Seizure | 45.3 | 23.8 | 53.7 |
| Syncope | 5.3 | 4.8 | 5.6 |
| Family History | 1 | 0 | 1 |

Table 2.2
Presenting symptoms

| Vascular Risk factors (Numbers) | | | |
|---|---|---|---|
| Hypertension | 10 | 8 | 2 |
| Diabetes | 5 | 5 | 0 |
| Hyperlipidaemia | 6 | 6 | 0 |
| Smoking or alcohol use | 10 | 10 | 0 |
| Thyroid angiopathy | 6 | 3 | 3 |

Table 2.3 Vascular Risk factors

| | |
|---|---|
| Mean MRS at presentation (over all) | 1.31 |
| Mean MRS at last follow-up | 0.7 |

Table2.4 MRS

Radiological characteristics.

| MRI | | | |
|---|---|---|---|
| Arterial Territorial Infarcts (hemispheres) | | 52 | |
| Hemispheric Infarcts (hemispheres) | | 19 | |
| Watershed infarcts (hemispheres) | | 30 | |
| Atrophy(hemispheres) | | 86 | |
| Ivy sign(in patients) | | 18 | |
| Type of involvement | ICA | ACA | MCA |
| **Stenosis** | 50 | 19 | 22 |
| **Occlusion** | 14 | 13 | 14 |
| | | | |
| Type | Basal | Dural | Pial |
| Collaterals(hemispheres) | 132 | 71 | 95 |

| **Radiologic Profiles of Hemispheres** | **Number** | **Percentage** |
|---|---|---|
| Suzuki stage | | |
| <3 | 65 | 43.3% |
| >3 | 85 | 56.7% |
| Posterior circulation involvement | 27 | 18% |

*Evaluation of vessels (Middle, Anterior, and Posterior Cerebral Arteries) with Preoperative Angiography for Steno-occlusive Lesions*

Table 3.1

Radiological characteristics.

## Surgical procedures

Combined revascularisation was the most common procedure, which was performed in 70 hemispheres. One patient had undergone an additional augmentation procedure with OA-MCA bypass with EDAMS. The combined procedures included STA-MCA bypass with EDAMS,OA-MCA bypass with EDAMS.

Table 3: Procedures

| Procedures | Patients | Hemispheres |
|---|---|---|
| Bilateral | 52 | |
| Bilateral Combined | 24 | 48 |
| Bilateral indirect | 18 | 36 |
| Bilateral mixed(combined and indirect on other side) | 10 | |
| Unilateral | 23 | |
| Unilateral Combined | 14 | 14 |
| Unilateral indirect | 9 | 9 |
| Combined | 48 | 72 |
| Indirect | 54 | 55 |

Table 4
Surgical procedures

## Treatment outcomes

Of the 75 patients, 52 had bilateral procedures,24 underwent bilateral combined,18 bilateral indirect. A total of 127 hemispheres were operated,54 patients underwent indirect revascularisation and 48 underwent combined procedures. There were 22 postoperative events. Post-operatively 9 developed stroke of which 6 were in combined group and 3 in indirect group. There was no significant difference in the rates of complications between the hemispheres with combined or indirect revascularization (12.5% vs 5 %p-0.2). Nine hemispheres experienced wound infections.

## Perioperative Complications

In the perioperative period 8 patient developed acute stroke,5 had TIA,3 patients developed seizures. There was SDH in 2 patients 1 patient had hyper perfusion injury. We had a mortality of two patients one from either procedural group cause of which was hemodynamic instability intraoperative and subsequent infarcts.

| Peri operative complications | Number |
|---|---|
| Stroke/Infarcts | 8 |
| TIA | 5 |
| Seizure | 3 |
| SDH | 2 |
| Death | 2 |
| Hyper perfusion | 1 |

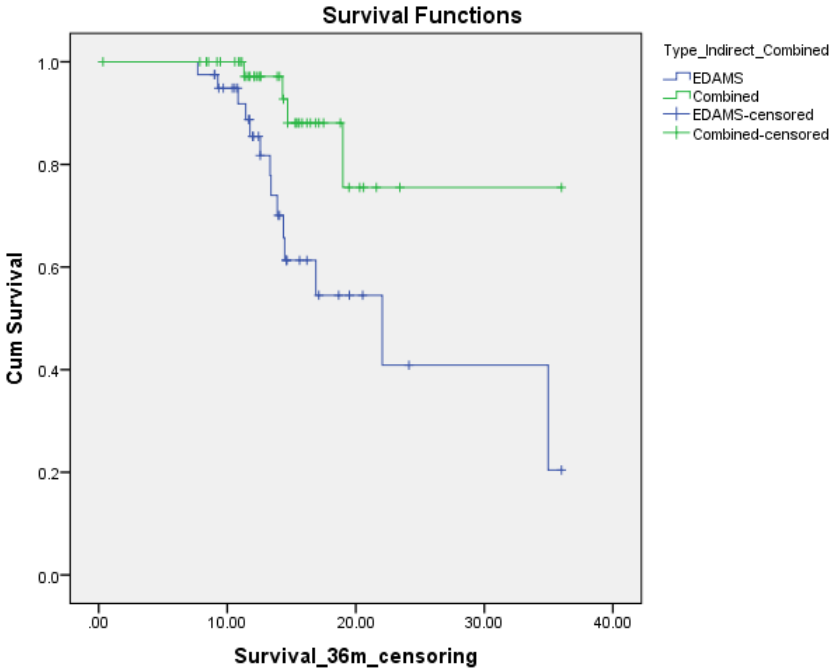
Table 5

Peri-operative complications

## Followup

There was an overall mean follow-up of 39 months. The median follow-up duration was 29 months, there were a total of 23 new events in 14 patients. In 70 hemispheres with combined procedures 7 (10 %) experienced postoperative events, whereas 16 of 57 (28%) hemisphere in indirect group had events. In hemispheres with Suzuki stage 3 or more, majority (17 of 23) of the postoperative events had occurred in follow-up period.

At 3 month (16%vs10.70 p.57) and 6 months (23% vs12.5%, p0.331) follow-up there was no statistically significant difference in the events between both the groups. A Kaplan Meier plot at 36 months shows that combined procedure has relatively less number of events than indirect procedure.


Survival Functions
Type_Indirect_Combined
EDAMS
Combined
EDAMS-censored
Combined-censored
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
.00
10.00
20.00
30.00
40.00
Survival_36m_censoring

Figure

# DISCUSSION

Moyamoya angiopathy (MMA) is a chronic progressive cerebrovascular occlusive angiopathy, Suzuki and Takaku introduced the term "moyamoya" in 1969 based on the cerebral angiographic appearance. There are only sporadic case reports, and only few institutional experiences reported in literature from India, and the exact incidence of MMA in India is unknown.

The angiopathy was thought to be endemic to Japanese islands and East Asian population but its incidence is increasingly reporting in southern part of India also.

The angiopathy shows a bimodal type of distribution in eastern population with peaks between 5 and 9 years, also 45 to 49 years. This study also demonstrated two peaks for age distribution but was lower compared to the results from Japan or Korea (<5years for children and 35-40 for adults respectively)

In eastern studies, the haemorrhagic manifestation of the angiopathy is described as <5% among the paediatric and 40% in adult MMA[vi] population. In North American series, haemorrhagic manifestation was reported in 2% of paediatric patients and in 1.7% of adult MMA patients. In our study haemorrhagic type of presentation was seen only in adult group. In our study the majority type of presentation was

ischemic (92%) in both adult and paediatric groups which is comparable to Japanese and American population. A higher female: male ratio was seen in North America (2.5:1) than in Asian countries(1.8–2.1:1) including Japan, Korea, China and Taiwan, a German institution demonstrated findings comparable to American studies by Kraemer et al[51] in 2008 with female-to-male preponderance was 4.25. in our study the overall female to male ratio is 2.5:1,which is slightly higher than that of the east Asian ratios.

Recurrent stroke is the most serious complication that worsens functional outcomes and increases mortality.

The goal of surgery is to prevent future stroke and diability in patients with MMA. Various studies shows that a combined revascularisation procedure is more effective for preventing future strokes.[37,38,39] Kim et al[35] in their study found that a direct or combined procedures for patients with moyamoya angiopathy helps in preventing further ischemic strokes.

Cho et al[36] in their study found that combined revascularization procedures resulted in clicnical, angiographic, and hemodynamic improvement in a way that was satisfactory over the long term, and interventions also prevented recurrent stroke.[43]

In our study also we found that for patients with MMA, combined

revascularization may be superior to indirect revascularization for prevention of follow up neurological events.

It has been seen in various studies that the incidence of newly developed cerebral infarction after indirect revascularization was somewhat higher than for the direct method or combined procedures.[40,41]

At last follow-up only one patient in our study had an unfavourable mRS and univariate analysis did not show any significant statistical association with post-operative events. Most of the patients showed improvement in mRS core irrespective of the procedure , indicating certain extent of revacualriation. Xincheng Zhang[44] in their study showed that preoperative cerebral infarction as an independent risk factor for perioperative stroke. Long-term cerebral rehemorrhage and the occurrence of perioperative complications were not associated with an improvement in the follow-up mRS (Modified Rankin Scale) score. Gross et al. in their series reported a higher annual incidence (5.4%) of postoperative strokes, in a shorter follow-up duration, and most of the post-operative strokes developed in the peri-operative period.[41] In our study also there were increased perioperative events in patients with combined procedure than indirect alone. This may be due to the local hyper perfusion, which has improved with short period of time.

Limitations of our study are the retrospective nature of the study and patients were recruited from single centre only. The occurrence of new clinical events were often not localised during follow-up either due recollection bias or lost followup. Long term follow-up imaging including DSA was not uniformly available, thus making it difficult to study the long term radiologic outcome

## Conclusion

A combined bypass procedure has shown to have a significant less number of events in post-operative follow-up period, when compared with indirect procedures. This study shows the importance of attempting a combined procedure for all patients with moyamoya irrespective of age group. This series also shows that revascularization procedures are effective in MMA, both in reducing further episodes of events and clinical improvement. Hence combined revascularization surgery should be the surgical option in all irrespective of age.

# ANNEXURES

*Curriculum Vitae*

*Appendices*

APPENDIX A – ETHICS COMMITTEE APPROVAL

APPENDIX B – PLAGIARISM CHECK REPORT

# Curriculum Vitae

| | | |
|---|---|---|
| SCARIA | SAM | |
| Last Name | First Name | Middle Name |
| Date of Birth (dd/mm/yy) 22/04/1989 | | Sex: male |
| Study Site Affiliaton-Co-lnvestigator | | |
| Professional Mailing Address<br>(Include Institution name) | | Study Site Address<br>(Include Institution name) |
| SamScaria<br>Resident, Department of Neurosurgery<br>SCTIMST, Trivandrum | | Department of Neurosurgery<br>SCTIMST, Trivandrum |
| Telephone (Office): | | Mobile Number:9497074582 |
| Telephone (Residence): | | Email:samscaria@rediffmail.com,<br>samscaria@sctimst.ac.in |

Academic Qualifications (Most recent qualification first)

| Degree/Certificate | Vear | Institution, Country |
|---|---|---|
| MBBS | 2015 | Government Medical College, Thrissur, India |
| | | |
| | | |
| | | |
| | | |

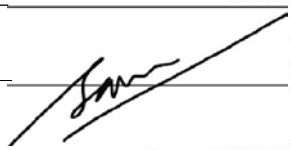
Details of professional registration : (MCI/State Registration/Bar Council/DCl/etc including Registration Number and Vear of Registration:TCMC-56277

Current and previous positions (most recent position first)

| Month and Vear | Title | Institution/Company, Country |
|---|---|---|
| January 2019 | Resident Neurosurqery | SCTIMST |
| May 2017-18 | Resident General Surqery | GMC Palakkad |
| March 2016-17 | Lecturer General Surgery | GMC Thrissur |
| | | |

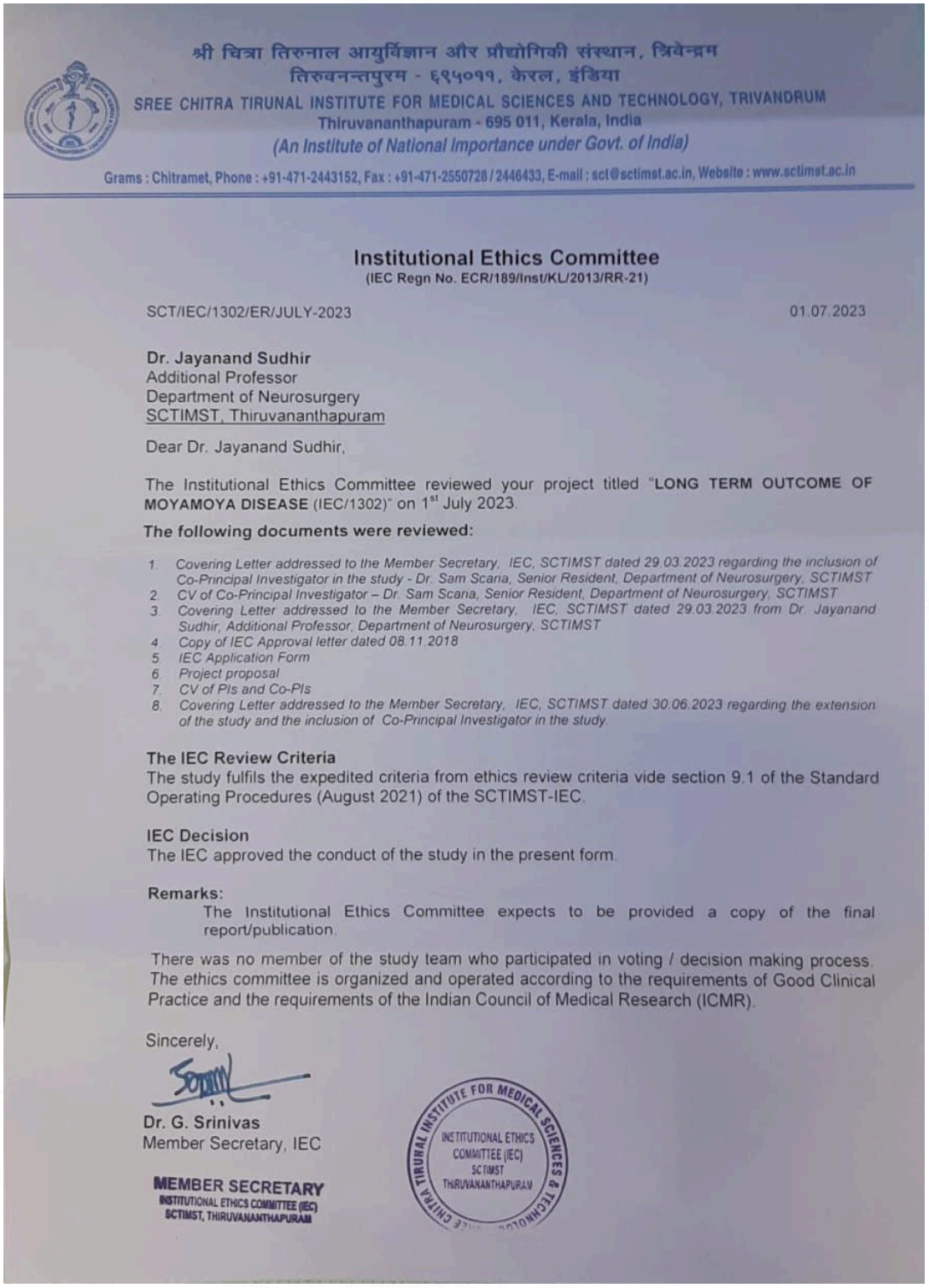
Brief summary of relevant research experience:
Synchronous Papillary Carcinoma of Thyroglossal Duct Cyst and Thyroid managed by a Single Transverse Neck Incision - A Case Report

Current project/s at

Signature: 

Date: 05/08/2019
Place:Trivandru

# APPENDIX A – ETHICS COMMITTEE APPROVAL



श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
*(An Institute of National Importance under Govt. of India)*
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**Institutional Ethics Committee**
**(IEC Regn No. ECR/189/Inst/KL/2013/RR-21)**

SCT/IEC/1302/ER/JULY-2023 01.07.2023

**Dr. Jayanand Sudhir**
Additional Professor
Department of Neurosurgery
SCTIMST, Thiruvananthapuram

Dear Dr. Jayanand Sudhir,

The Institutional Ethics Committee reviewed your project titled "**LONG TERM OUTCOME OF MOYAMOYA DISEASE** (IEC/1302)" on 1st July 2023.

**The following documents were reviewed:**

1. *Covering Letter addressed to the Member Secretary, IEC, SCTIMST dated 29.03.2023 regarding the inclusion of Co-Principal Investigator in the study - Dr. Sam Scaria, Senior Resident, Department of Neurosurgery, SCTIMST*
2. *CV of Co-Principal Investigator – Dr. Sam Scaria, Senior Resident, Department of Neurosurgery, SCTIMST*
3. *Covering Letter addressed to the Member Secretary, IEC, SCTIMST dated 29.03.2023 from Dr. Jayanand Sudhir, Additional Professor, Department of Neurosurgery, SCTIMST*
4. *Copy of IEC Approval letter dated 08.11.2018*
5. *IEC Application Form*
6. *Project proposal*
7. *CV of PIs and Co-PIs*
8. *Covering Letter addressed to the Member Secretary, IEC, SCTIMST dated 30.06.2023 regarding the extension of the study and the inclusion of Co-Principal Investigator in the study.*

**The IEC Review Criteria**
The study fulfils the expedited criteria from ethics review criteria vide section 9.1 of the Standard Operating Procedures (August 2021) of the SCTIMST-IEC.

**IEC Decision**
The IEC approved the conduct of the study in the present form.

**Remarks:**
The Institutional Ethics Committee expects to be provided a copy of the final report/publication.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

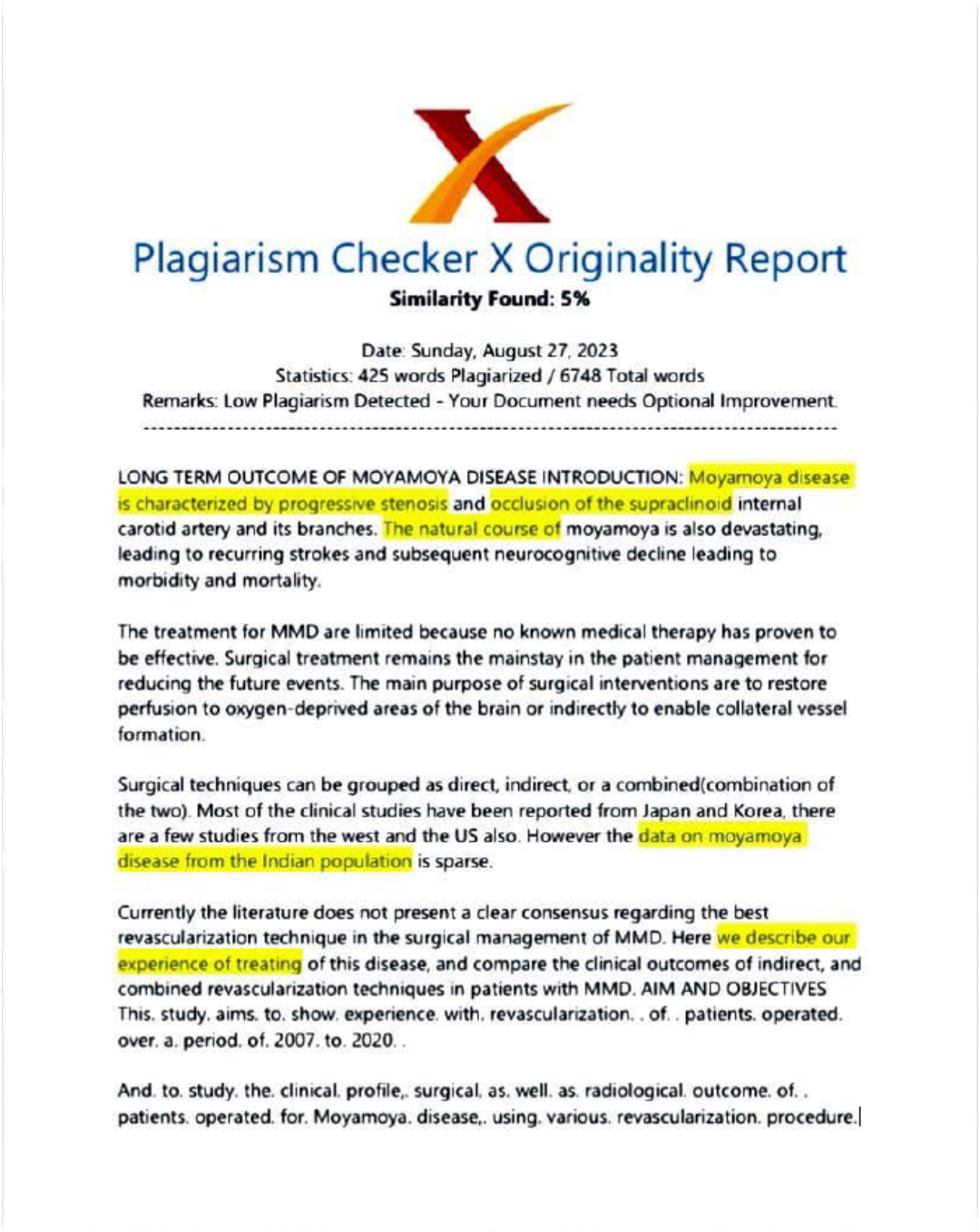
Sincerely,

Dr. G. Srinivas
Member Secretary, IEC

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST, THIRUVANANTHAPURAM

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST
THIRUVANANTHAPURAM

# APPENDIX B – PLAGIARISM CHECK REPORT



Plagiarism Checker X Originality Report

**Similarity Found: 5%**

Date: Sunday, August 27, 2023
Statistics: 425 words Plagiarized / 6748 Total words
Remarks: Low Plagiarism Detected - Your Document needs Optional Improvement.

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LONG TERM OUTCOME OF MOYAMOYA DISEASE INTRODUCTION: Moyamoya disease is characterized by progressive stenosis and occlusion of the supraclinoid internal carotid artery and its branches. The natural course of moyamoya is also devastating, leading to recurring strokes and subsequent neurocognitive decline leading to morbidity and mortality.

The treatment for MMD are limited because no known medical therapy has proven to be effective. Surgical treatment remains the mainstay in the patient management for reducing the future events. The main purpose of surgical interventions are to restore perfusion to oxygen-deprived areas of the brain or indirectly to enable collateral vessel formation.

Surgical techniques can be grouped as direct, indirect, or a combined(combination of the two). Most of the clinical studies have been reported from Japan and Korea, there are a few studies from the west and the US also. However the data on moyamoya disease from the Indian population is sparse.

Currently the literature does not present a clear consensus regarding the best revascularization technique in the surgical management of MMD. Here we describe our experience of treating of this disease, and compare the clinical outcomes of indirect, and combined revascularization techniques in patients with MMD. AIM AND OBJECTIVES This. study. aims. to. show. experience. with. revascularization. . of. . patients. operated. over. a. period. of. 2007. to. 2020. .

And. to. study. the. clinical. profile,. surgical. as. well. as. radiological. outcome. of. . patients. operated. for. Moyamoya. disease,. using. various. revascularization. procedure.

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