PERFUSION PATTERNS IN VARYING ANGIOGRAPHIC STAGES (SUZUKI GRADING) OF INDIAN MOYAMOYA PATIENTS

Dr SAMBHA MURTHY KRISHNA MOHAN MAVURU

DM NEUROLOGY THESIS

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A THESIS SUBMITTED BY

Dr SAMBHA MURTHY KRISHNA MOHAN MAVURU

TO

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE AWARD OF

DM (NEUROLOGY)

2021-2023

DECLARATION BY THE STUDENT

CERTIFICATE

I, Dr Sambha Murthy Krishna Mohan Mavuru, hereby certify that I had personally carried out the workdepicted in the thesis titled "Perfusion patterns in varying angiographic stages (Suzuki grading) of Indian Moyamoya patients".

Nopart of this thesis has been submitted for the award of any other degree or diploma prior to this date.

Date: 25.8.23

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The thesis entitled, "Perfusion patterns in varying angiographic stages (Suzuki grading) of Indian Moyamoya patients". 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.

*Clearance was obtained from the Institutional Ethics Committee for carrying out the study.

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APPROVAL OF THE THESIS

The thesis entitled

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for the degree of **DM**

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Dr S M Krishna Mohan M

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LIST OF ABBREVIATIONS

S.No.	Abbreviation	Full form
1.	MMD	Moyamoya disease
2.	DSA	Digital subtraction angiography
3.	MRI	Magnetic resonance imaging
4.	MR-ASL	Magnetic resonance -Arterial Spin Labelling
5.	ICA	Internal carotid artery
6.	MMS	Moyamoya syndrome
7.	SNP	Single nucleotide polymorphism
8.	RNF 213	Ring finger protein 213
9.	TGF-B1	Transforming growth factor Beta 1
10.	VEGF	Vascular endothelial growth factor
11.	MMP	Matrix metalloproteinase
12.	HGF	Hepatocyte growth factor
13.	IL	Interleukin
14.	TIA	Transient ischemic attack
15.	MCA	Middle cerebral artery
16.	ACA	Anterior cerebral artery
17.	PCA	Posterior cerebral artery
18	CT	Computed tomography
19.	MR-VWI	Magnetic resonance vessel wall imaging
20.	PET	Positron emission tomography

21.	Xe-CT	Xenon-enhanced CT scan
22.	SPECT	Single photon emission computed tomography scan
23.	ASL	Arterial spin labelling
24.	PLD	Post labelling delay
25.	CASL	Continous Arterial spin labelling
26.	pCASL	Pseudo-continous Arterial spin labelling
27.	PASL	Pulsed arterial spin labelling
28.	CTP	Computed tomography perfusion scan
29.	CBF	Cerebral blood flow
30.	DSC	Dynamic Susceptibility Contrast
31.	EMR	Electronic Medical Records
32.	PACS	Picture Archiving and Communication System
33.	NF-1	Neurofibromatosis
34.	NIHSS	National Institute for Health Stroke Scale
35.	mRS	Modified Rankin Scale
36.	CCA	Common carotid artery
37.	ECA	External Carotid artery
38.	VA	Vertebral Artery
39.	ASL-SIR	Arterial spin labelling Signal Intensity Ratio
40.	ROI	Region Of Interest
41.	BG	Basal Ganglia
42.	M1	Middle cerebral artery cortical territory at basal ganglia level in the insular region

43.	M2	Middle cerebral artery cortical territory above basal ganglia level in the perirolandic region
44.	A1	Anterior cerebral artery cortical territory at basal ganglia level in the parasagittal frontal region
45.	A2	Anterior cerebral artery cortical territory above basal ganglia level in the paracentral lobule region
46.	P1	Posterior cerebral artery cortical territory at basal ganglia region in the mesial occipital region
47.	P2	Posterior cerebral artery cortical territory above basal ganglia region in the mesial posterior parietal region
48.	ATA	Arterial Transit Time
49.	MTT	Mean Transit Time

SYNOPSIS

Imaging plays a crucial role in the diagnosis and prognostication of patients with Moyamoya disease (MMD). The gold standard DSA comes with the pitfalls of cumbersome procedure, risk of exposure to contrast and radiation, and requiring expertise. It has long been known that with progressive steno-occlusive disease, collaterals develop to mitigate the ischemia. However, this was not demonstrated with functional studies in MMD. Newer imaging modalities without the drawbacks of DSA have been the areas of interest for a long. The current study aimed to use the MR-ASL technique to demonstrate the functional change (i.e. the change in perfusion with a change in collateral status at various brain regions across various stages of severity of MMD) and its utility in predicting the collaterals compared to DSA.

This was a single-center observational cohort study with retrospective and prospective arms where consecutive MMD patients with DSA and MR-ASL done within 3 months of each other were included. A total of 46 patients with 88 hemispheres (4 hemispheres which were operated were excluded) were included in the final analysis. Both the DSA and the MR-ASL images of all these patients were reviewed by two neuroradiologists. The severity of the MMD was graded according to Suzuki staging on DSA. Collaterals were graded in 7 different regions of the brain (BG, M1, M2, A1, A2, P1, P2) both in DSA and MR-ASL using a 4-point grading system (except in BG on MR-ASL where only 3-point grading was used). Also, ASL-SIR was used as a quantitative measure to quantify the perfusion instead of direct CBF measurement.

The study has shown that with the progression of the severity of the disease, the collaterals appear and disappear at different regions, i.e. the perfusion deficit in MMD is dynamic. The collaterals were maximum in the basal ganglia region and were maximum in

Suzuki stage 3, and with further disease progression, they disappeared. The collaterals appeared late in the disease course in the superficial cortical surfaces due to pial-pial and ECA collaterals development. The change in collaterals was accompanied by a change in the perfusion deficit as demonstrated by the MR-ASL technique. This change in collaterals with the disease progression was statistically significant. Also, the study has shown that the MR-ASL technique can be reliably used to predict collateralization compared to DSA. The study showed a strong agreement in the collateral scores done on DSA and MR-ASL techniques which was statistically significant.

Thus, the study showed a changing perfusion deficit in different brain regions depending on the severity of the MMD using MR-ASL technique. Also, the MR-ASL technique can be used to predict the collaterals in MMD patients which is comparable to DSA.

INTRODUCTION

Moyamoya Disease (MMD) is a rare chronic progressive steno-occlusive disease of intracranial internal carotid arteries and their proximal branches (Kuroda and Houkin, 2008), of unknown etiology, presenting with various clinical manifestations in pediatric and adult populations. It is a rare disease worldwide but is more commonly seen in East Asian countries, with an annual incidence of 0.5-1.5 per 100,000 individuals. In contrast, the incidence in North America is estimated to be only 0.1 per 100,000 (Uchino et al., 2005). Also, it was noted that this disease is more common among Asian Americans compared to Hispanics in the American population, making it a predominant disease of the East Asian countries (Uchino et al., 2005). Also, various studies confirmed this gradient in incidence between East and West across the globe (Shang et al., 2020). Various aspects of the disease have been studied extensively since the time of its discovery in 1957 (Suzuki, 1969) in countries with high prevalence, like Japan, but there are many areas that need explanation and research, especially regarding the tissue perfusion patterns and mechanisms.

The incidence of MMD in India is not exactly known, and it is a diagnosis rarely made in our clinics. Understanding the disease pathophysiology is vital in elucidating better management options for these patients. It is imperative that with progressive stenosis, hypoperfusion occurs and subsequent collateralization occurs to mitigate the same (Schubert et al., 2014). However, depending on the stage of the disease whether the perfusion patterns follow this hypothesis was never studied before in detail.

Digital subtraction angiography (DSA) is the gold standard for diagnosing and staging MMD. However, it is an invasive procedure that involves the use of contrast agents and radiation exposure. It is also challenging to use for serial monitoring or in uncooperative

patients. Hence, alternate methods to look at the tissue perfusion in determining patient management are warranted. Various Magnetic resonance imaging (MRI) techniques have been tried in the past (Calamante et al., 2001; Togao et al., 2006; Zaharchuk et al., 2011), but each has its limitations, like the usage of contrast agents, which raises problems, especially in pediatric cases in whom this disease is common. Magnetic resonance -Arterial Spin Labelling (MR-ASL) has been studied previously to predict the collateral status compared to gold standard DSA (Zaharchuk et al., 2011). Techniques other than MRI have also been used to study the perfusion status in these patients (Schubert et al., 2014; Yin et al., 2018), but their availability and contrast usage limit their routine use in clinical practice.

Aims and Objectives:

Null Hypothesis:

The perfusion deficit in Moyamoya disease is dynamic. Non-invasive techniques like MR-ASL can be used to quantify and follow-up these patients

Aim/goal:

The purpose of this study is to:

1. To evaluate perfusion patterns in patients with MMD

2. To compare the perfusion patterns in different angiographic stages of MMD

3. To compare the utility of the MR-ASL technique in predicting the perfusion and collateral status as compared to gold standard DSA

Scope of the study:

Our study hopes to look into the utility of the MR-ASL technique to identify the collateral status in MMD patients depending on their Suzuki stage determined by DSA, to look if the perfusion patterns follow the Suzuki staging, and to determine if MR-ASL can be used an alternative for DSA in determining the collaterals and serial follow-up in these patients.

The following sections cover the existing literature in detail, the complete methodology, thorough results and succinct discussion of the study results.

REVIEW OF LITERATURE

Moyamoya disease (MMD) is a non-atherosclerotic vasculopathy characterized by progressive stenosis or occlusion of the intracranial internal carotid arteries (ICA) and their proximal branches, with subsequent abnormal collateral vessel development. (Shang et al., 2020) Takeuchi et al. were the first ever to describe this clinical entity in 1957 when they called it "hypoplasia of bilateral internal carotid arteries." However, it was later recognized as an acquired and progressive disease rather than an inherited static disease. (Demartini Jr. et al., 2022) The first use of the term 'Moyamoya' dates back to 1969, when Suzuki et al. coined this term, which in Japanese would mean 'hazy like a puff of smoke' due to its angiographic appearance caused by sprouting collaterals. (Suzuki, 1969) Furthermore, this nomenclature is ICD recognized by the code I67.5. When MMD occurs as a part of another genetic syndrome, it is termed moyamoya syndrome (MMS).

Epidemiology

MMD is a disease found worldwide in varied ethnic and genetic backgrounds. However, it is evident from the studies that this is a disease of Asian descent, and more particularly of East Asian ethnicity, mainly Japanese, Korean, and Chinese. Even in the USA, the disease is more common among patients of Asian descent. (Demartini Jr. et al., 2022; Uchino et al., 2005) The data regarding the epidemiology from India is scarce due to the rarity of the diagnosis and the lack of prospective databases looking at this uncommon disease. Only small case series and retrospective cohort studies are available regarding Indian MMD patients. (Das et al., 2022; Sadashiva et al., 2016; Sreenivasan et al., 2022; Sundaram et al., 2014) Das et al. (Das et al., 2022), in their single-center study from East India, where five years of retrospective data of 10,250 consecutive stroke patients showed a frequency of Moyamoya

angiopathy in 1.56% of patients. Lack of awareness regarding this disease entity among health care providers also leads to assumed low prevalence due to misdiagnosis. A single-center retrospective study from Germany showed that up to 62% of MMD cases had initial misdiagnosis. (Graf et al., 2019) Studies from East Asian countries and the USA showed higher incidence among females. From the studies in India, the Eastern Indian cohort has female preponderance, while studies from central and southern India had no significant difference in male and female patient numbers. (Das et al., 2022; Demartini Jr. et al., 2022; Kim, 2016; Sadashiva et al., 2016; Sreenivasan et al., 2022; Sundaram et al., 2014; Uchino et al., 2005) Large population-based studies are required to determine the true epidemiology of MMD in India. MMD can affect individuals of all age groups. Bimodal incidence has been described with MMD where the first peak occurs at 5-14 years of age and the second at 45-54 years of age. (Kim, 2016) Thus, MMD also forms an important cause of stroke in the pediatric age group and young stroke.

Etiology and pathogenesis

The exact pathomechanisms and etiological factors in the development of MMD are not entirely understood and are thought to be multifactorial due to the interaction of genetic, environmental, and vessel-related mechanical factors.

Single nucleotide polymorphisms (SNP) in the gene encoding for Ring finger protein 213 (RNF 213) on chromosome 17q25.3 are found to confer genetic susceptibility for cerebrovascular disease. (Wang et al., 2018) RNF 213 p.R4810K variant is found to be associated with MMD in people of Asian ancestry. This association was also proven in the Indian population. (K. et al., 2020) Since this SNP was identified in MMD patients, various hypotheses to explain the pathobiology of this gene leading to disease were postulated, including its action as a metabolic gatekeeper in lipid metabolism, coordinator of cellular

response to hypoxia, and ubiquitination pathways.(Ahel et al., 2020; Wang et al., 2018) It is also thought to be important in maintaining vascular endothelial integrity. (Roy et al., 2022) Other genetic determinants are poorly understood including HLA association, genes coding for Transforming growth factor beta-1 (TGF-B1), Vascular endothelial growth factor (VEGF), Matrix metalloproteinases (MMP) 2,3 and 9, and few genetic loci on 3p, 17q, etc. (Mertens et al., 2022)

Various cytokines, including VEGF, TGFB, and Hepatocyte growth factor (HGF), are postulated to have a role in MMD pathogenesis as they are expressed in amounts higher than in healthy subjects. (Shang et al., 2020) An autopsy study of 3 MMD patients has shown increased and abnormal expression of S100A4 protein and IgG in the vascular smooth muscles that have migrated into the intima. (Lin et al., 2012) CD34+ cells, Th17 cells, and other proinflammatory markers like IL-6, TGFB1, and IL17 were found to be higher in MMD patients compared to healthy controls. (Lin et al., 2012; Ni et al., 2011; Weng et al., 2017) Tanghetti et al. reported MMD in only one of the identical twins, thus leaving a lacuna beyond genetic susceptibility in the pathogenesis of MMD.(Tanghetti et al., 1983) Even with strong susceptibility with certain genes, familial association, and ethnic predisposition, not all first degree relatives develop MMD. Thus, the role of environmental factors cannot be ruled out with the current knowledge. All the above mechanisms culminate in intimal thickening, smooth muscle hyperplasia, thinned-out media, and disruption of internal elastic lamina without obvious histopathological evidence for inflammation or atherosclerosis.(Lin et al., 2012; Shang et al., 2020)

With the postulated genetic and inflammation-mediated pathways, the question of why distal ICAs alone are most prone to disease remains unexplained. Sudhir et al. have postulated a unifying hypothesis of mechanobiological theory for the pathogenesis of MMD based on

their systematic review. (Sudhir et al., 2021) In the mysterin (another name for RNF 213) deficient zebra fish larvae model, impaired neuromuscular regulation due to absent mysterin led to the delayed extension of the head over the trunk along with abnormal and excess sprouting of vessels. But the proximal large vessel formation was normal in these larvae. (Kotani et al., 2015; Liu et al., 2011) Similar analogous changes in humans were postulated to have caused abnormal cavernous-supraclinoid angle of ICA in MMD patients with RNF 213 SNPs, along with stretching and loss of tortuosity of ICA. These, in turn, lead to excess shear stress on the vessel wall, which, combined with increased metalloproteinases, altered blood viscosity, and associated inflammation, will culminate in pathological changes of MMD.(Sudhir et al., 2021) The association of collagen diseases like Marfan syndrome, Ehler-Danlos syndrome, sickle cell disease, and thrombophilias with Moyamoya vasculopathy supports this hypothesis.

Clinical features of MMD

MMD can present with either cerebral ischemia (ischemic stroke or transient ischemic attack[TIA]) or hemorrhage. Ischemic symptoms are attributed to the reduced blood supply due to steno-occlusive disease affecting the proximal ICAs. The hemorrhage is thought to occur due to rupture of immature and excess collaterals or aneurysms formed due to ischemia and abnormal shear stress of the vessel wall.(Scott and Smith, 2009) The MMD affects most commonly the middle cerebral artery (MCA) followed by the anterior cerebral artery (ACA); the corresponding vascular territories involving frontal, parietal, and temporal lobes are the most affected areas. So, limb weakness, speech abnormalities, including dysarthria and aphasia, are the common presentations. Seizures are the next common manifestation in these patients. Other less common presentations include cognitive impairment, visual deficits, syncope, and headache. The accompanying personality changes in some may cause

misdiagnosis of psychiatric illness. (Scott and Smith, 2009) Clinical manifestations described in Indian studies are also similar.(Sadashiva et al., 2016; Sreenivasan et al., 2022; Sundaram et al., 2014)

Various precipitating factors for ischemic events in MMD were described. Common ones include hyperventilation, crying, dehydration, and anesthesia used for even minor procedures or severe exertion. This is presumed to be due to reduced cerebral perfusion secondary to reduced intravascular volume or sudden constriction in already maximally dilated diseased collateral vessels. (Das et al., 2023; Scott and Smith, 2009) Das et al., in their study, found out fever, emotional stress, heavy exercise, and diarrhea are the common precipitants of symptoms in MMD patients. (Das et al., 2023)

Hemorrhagic stroke is seen in up to 1/3rd of MMD patients and is more commonly described in adults than in children. The association of higher age with hemorrhagic presentation in MMD patients is consistent in Indian studies as well. (Das et al., 2022; Sadashiva et al., 2016; Shang et al., 2020; Sreenivasan et al., 2022) The clinical manifestations depend on the location of the bleed, which can vary from parenchymal, intraventricular or subarachanoid space. Bleeds may be more commonly seen with arteries involving the posterior circle of Willis due to the hypothesis that these arteries are at increased risk for higher vessel wall shear stress, thus leading to a higher percentage of aneurysms and bleeds. Headaches in MMD patients are likely due to vasodilatation of meningeal collateral vessels. Thus, the headache character is mostly similar to migraine in these patients. Chorea is an uncommon manifestation due to the development of basal ganglia collaterals. (Scott and Smith, 2009)

The Moyamoya disease is classically known to be a disease afflicting bilateral hemispheres. However, unilateral cases have been described, which were initially thought to be a subtype of MMS, even in the absence of other identifiable associated diseases or risk

factors. Hayashi et al. found unilateral MMD presents with a mean age of 39 years with female preponderance, while pediatric cases tend to become bilateral on follow-up. (Hayashi et al., 2010; Kelly et al., 2006)

Diagnosis of MMD

Radiology plays a pivotal role in MMD diagnosis. When patients present with acute manifestations, CT or MRI brain is the first line investigation usually done. The CT or MR angiography may show the steno-occlusive nature of the disease. These investigations also reveal infarcts or bleed, either acute or chronic. Ivy sign on MRI is thought to be a characteristic sign for MMD, which indicates the compensatory leptomeningeal collaterals.(Sivrioglu et al., 2016) Digital subtraction angiography (DSA) is mandatory for the diagnosis of MMD. DSA is considered the gold standard investigation for this purpose. After the DSA is done, the disease severity is graded using the Suzuki staging system.(Suzuki and Kodama, 1983) This staging system was first devised in 1971 by Suzuki et al. and has been used for more than half a century, even today. This staging not only gives the picture of the progressive steno-occlusive disease but also characterizes the extent of the collaterals.

But DSA being an invasive test involving contrast agent, people have tried to devise other modalities to visualize the disease process. Notable of this is magnetic resonance vessel wall imaging (MR-VWI), which can be used to differentiate between various intracranial vasculopathies, especially when there is isolated focal stenosis. The involved segment shows concentric thickening with concentric contrast enhancement and negative remodeling without juxtaluminal T2 hyperintensity. (Adhithyan et al., 2018)

Perfusion studies in MMD

Modalities measuring the perfusion, like Xe-CT scan (Xenon enhanced CT scan),

positron emission tomography (PET), single photon emission CT (SPECT), etc, were variably used to measure the perfusion deficit developing with disease progression in MMD. (Hara et al., 2022; Togao et al., 2023, 2006; Zaharchuk et al., 2011) Nevertheless, limited availability of these techniques and the use of contrast in some of them puts them at a disadvantage. So, efforts were made to include Magnetic resonance arterial spin labeling (MR-ASL), a readily available and reproducible MRI sequence to predict perfusion in MMD patients. The advantages of MR-ASL are that it does not require contrast and can be acquired in a short time, thereby reducing the need for sedation as compared to standard DSA. Also, it is included with the most newer MRI machines, thus increasing its availability. (Grade et al., 2015)

ASL technique employs magnetic labeled water molecules as an 'endogenous tracer' instead of an external contrast agent. The magnetic label is given at the upper neck to the blood in the carotids, and the decay of the magnetization is measured at the target site. The biggest disadvantage of ASL is the low signal-to-noise ratio because of the fluctuating signal from static tissue because of physiologic or thermal effects. Due to this reason, ASL requires longer acquisition times and is also susceptible to motion artifacts. Once a label is given, the water molecules in the blood reach the target tissue, and the time lapsed during this process is called post-labeling delay (PLD). The t1 relaxation time of these water molecules is measured in the target tissue. This signal is also transferred to surrounding water molecules and static tissue. Keeping this into account, different types of ASL sequences were developed: continuous ASL (CASL), pseudo-continous ASL (pCASL), and pulsed ASL (PASL). (Grade et al., 2015)

Various studies have looked into the utility of ASL in MMD patients. Zaharchuk et al. showed good agreement between collaterals determined by DSA and ASL, and ASL collateralization is proportional to the CBF measured by ASL and Xe-CT scans. (Zaharchuk et al., 2011) In 2014, Wang et al. studied 4 PLD pCASL in 17 patients with moyamoya disease

and compared it with computed tomography perfusion (CTP). They showed a significant association between the perfusions measured by subjective ratings and voxel-wise analysis in different regions of interest using normalized perfusion means. (Wang et al., 2014) Fan et al., in 2017, studied different ASL techniques' utility in estimating CBF compared to 15O-PET scans in 15 moyamoya patients. They showed that standard delay ASL acquisition has underestimated the CBF. When multi-delayed ASL was obtained, there was increased consistency in predicting CBF compared to PET scan, but underestimation was still noted. Long-label long-delay ASL showed the maximum correlation with 15O-PET scan. (Fan et al., 2017) Recently, 3D pCASL was shown to be comparable in assessing the perfusion status of the brain in MMD patients compared to dynamic susceptibility contrast (DSC-MRI) by Zhang et al. in their study, which included 174 MMD cases. (Zhang et al., 2022) In a most recent study, Togao et al. showed a moderate but significant correlation in CBF values when measured using dynamic pseudo-continuous arterial spin labeling and SPECT. (Togao et al., 2023)

Change in collaterals with disease progression

Yamamoto et al. have looked into the relationship between collateral shifting and hemorrhagic presentation in MMD patients. Among the 71 hemispheres from the 41 MMD cases, they showed the collaterals shift from anterior to posterior, i.e., from lenticulostriate and anterior choroidal artery towards posterior communicating artery and posterior choroidal artery. This was shown by using collateral grading from 0 to 3 – a qualitative measure across all MMD stages in all four arteries of interest. They also showed that this shift was indeed associated with progressing age and was shown to be a predictor for hemorrhagic stroke in them. (Yamamoto et al., 2019)

MATERIALS AND METHODS

Study design

This was a hospital based observational cohort study with both prospective and retrospective arms. For the retrospective arm, MMD patients were recruited from the electronic medical records (EMR) from January 2016 to December 2021 were included, if they fulfilled the inclusion criteria. Cases from 2016 were included as MR-ASL technique was introduced in the institute from 2016. For the prospective arm of the study, MMD patients were consecutively recruited from the neurology wards, between January 2022 to March 2023 if they satisfied the inclusion criteria.

Patients

Inclusion criteria:

Patients diagnosed with MMD who have underwent DSA either at our hospital or elsewhere, and with MR-ASL done from our hospital within 3 months of one another, and images are available for review in the institution picture archiving and communication (PACS) system were included.

Patients of all age groups and both the sexes were included. All the patients who fulfil the inclusion criteria were recruited into the study by the principal and co-principal investigator after taking the informed consent from either the patient or from the care giver in case of pediatric cases. For the retrospectively included patients, consent was waived by the institutional ethics committee.

Exclusion criteria:

- In the patients who have already underwent revascularization procedure on one side, then the corresponding hemisphere was excluded. If MR-ASL is obtained after revascularisation patient was not included
- Patients with associated sickle cell disease, Neurofibromatosis (NF 1), Down's syndrome, history of cranial therapeutic irradiation, hyperthyroidism, renal artery stenosis, giant cervicofacial hemangiomas, congenital cardiac anomalies.
- Patients with pre-operative MRI done from other hospitals or institutions before being referred to our institute for further management
- Claustrophobic patients and patients who could not undergo MRI
- Patients whose images were not available for analysis

Study population:

The number of patients who had MMD were 65 in the retrospective arm and 19 in the prospective arm. Finally, 46 patients were included (37 patients in the retrospective arm and 9 patients in the prospective arm of the study (Figure 1).

The study was started only after the institutional ethics committee approval. Informed consent was waivered for the retrospectively included patients and it was obtained from the prospectively included patients.

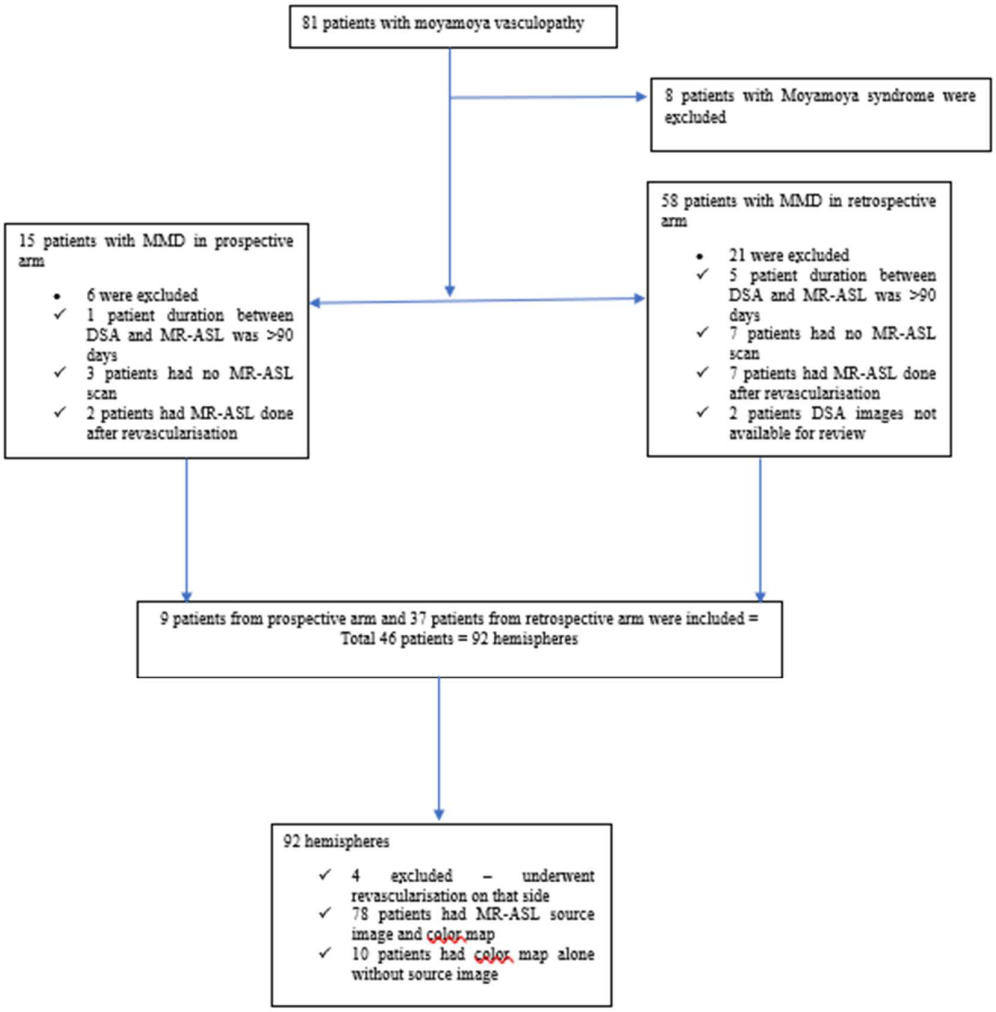

Figure 1: Patient recruitment flowchart

Demographics and clinical history:

The gender and demographic characteristics were recorded for all patients. The clinical data of the retrospectively included patients was retrieved from the electronic medical records (EMR). For the prospectively included patients, it was collected from the patients and their bystanders.

The clinical history details recorded include the age, gender, type of presentation, clinical symptoms of the patient, admission NIHSS and mRS, and the interval between DSA and MR-ASL scans.

Imaging analysis:

The MR-ASL sequence was acquired on a GE 3T discovery 750W scanner (GE healthcare, Milwaukee, WI, USA). In ASL, tagging was done using the pseudocontinuous technique (pCASL). The labelling plane was placed in the upper part of the neck, about 2-2.5cm lower to the inferior most slice of the acquisition plane. The acquisition time was about 5 mins. The slice thickness of the 3D pseudocontinous ASL was 4mm, field of view was 24 x 24cm, time to repetition was 4850millisec, time to echo was 10.7 millisecs. The post labeling delay was varied depending on the age of the patient. For pediatric patients, it was about 1525 millisecs and for adult patients it is 2025 millisecs.

The DSA was done under local or general anesthesia depending on patient co-operation and patient general condition. Seldinger technique was used for access of the common femoral artery and selective angiograms of the both common carotid arteries (CCAs), internal carotid arteries (ICAs), external carotid arteries (ECAs) and the vertebral arteries (VAs) were obtained. If DSA done at another hospital was available, that was analysed without repeating another DSA at our institute.

The DSA and the MR-ASL images in the PCAS were reviewed by two Radiologists (VK and BT) after being blinded to the clinical findings. Each investigator has rated the DSA and ASL scans independently and the disagreements were resolved by consensus. Both the DSA and ASL were analysed for each hemisphere independently. The severity of the MMD was determined by Suzuki grading (Table 3.1).

Table 1: Suzuki Grading

Grade 1	Narrowing of ICA apex
Grade 2	Initiation of Moyamoya collaterals
Grade 3	Progressive ICA stenosis with intensification of Moyamoya associated collaterals
Grade 4	Development of ECA collaterals
Grade 5	Intensification of ECA collaterals and reduction of Moyamoya associated collaterals
Grade 6	Total occlusion of ICA and disappearance of Moyamoya associated collaterals

For the qualitative collateral assessment on DSA and ASL, a total of 7 regions in each hemisphere were analysed (figure 1-6). These 7 regions were:

1. BG – basal ganglia
2. M1 – in the MCA cortical territory at basal ganglia level in the insular region
3. M2 – in the MCA cortical territory above basal ganglia level in the perirolandic region
4. A1 – in the ACA cortical territory at basal ganglia level in the parasagittal frontal region
5. A2 – in the ACA cortical territory above basal ganglia level in the paracentral lobule region
6. P1 – in the PCA cortical territory at basal ganglia level in the mesial occipital region
7. P2 – in the PCA cortical territory above basal ganglia level in mesial posterior parietal lobe.

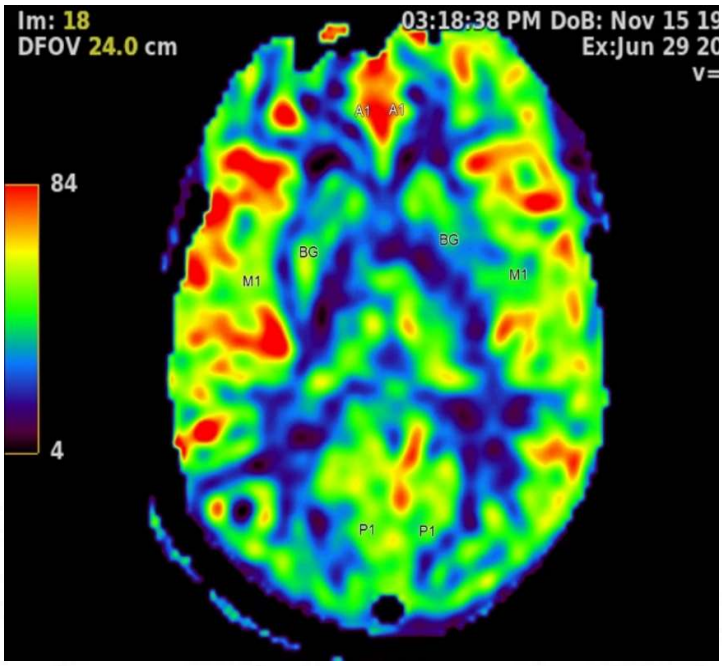

Figure 2 – Regions used for grading collaterals at basal ganglia level on ASL – depicting BG, M1, A1 and P1 regions on both sides.

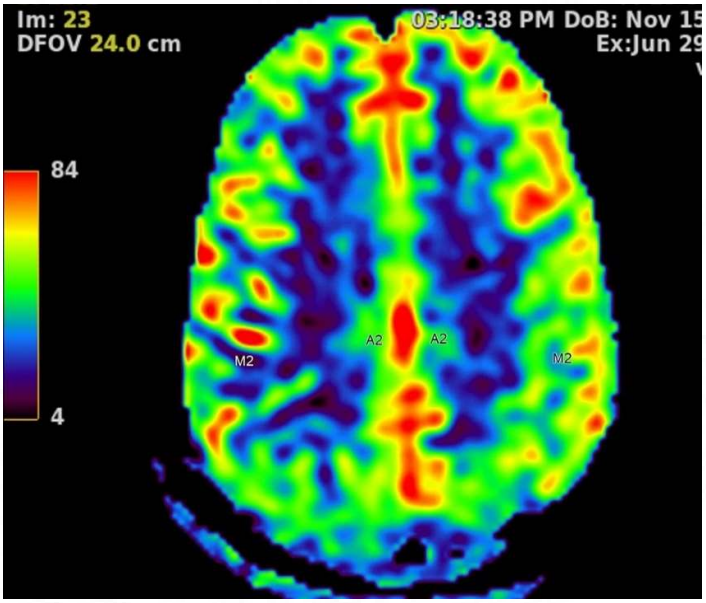

Figure 3: Regions used for grading collaterals on ASL above the basal ganglia level – depicting M2 and A2 on both sides

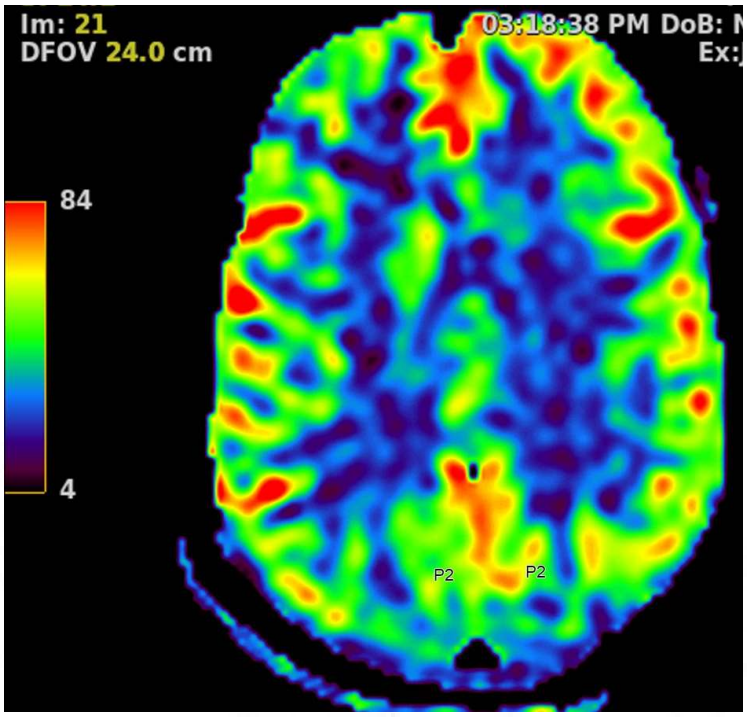

Figure 4: Regions used for grading collaterals on ASL above the basal ganglia level – depicting P2 on both sides

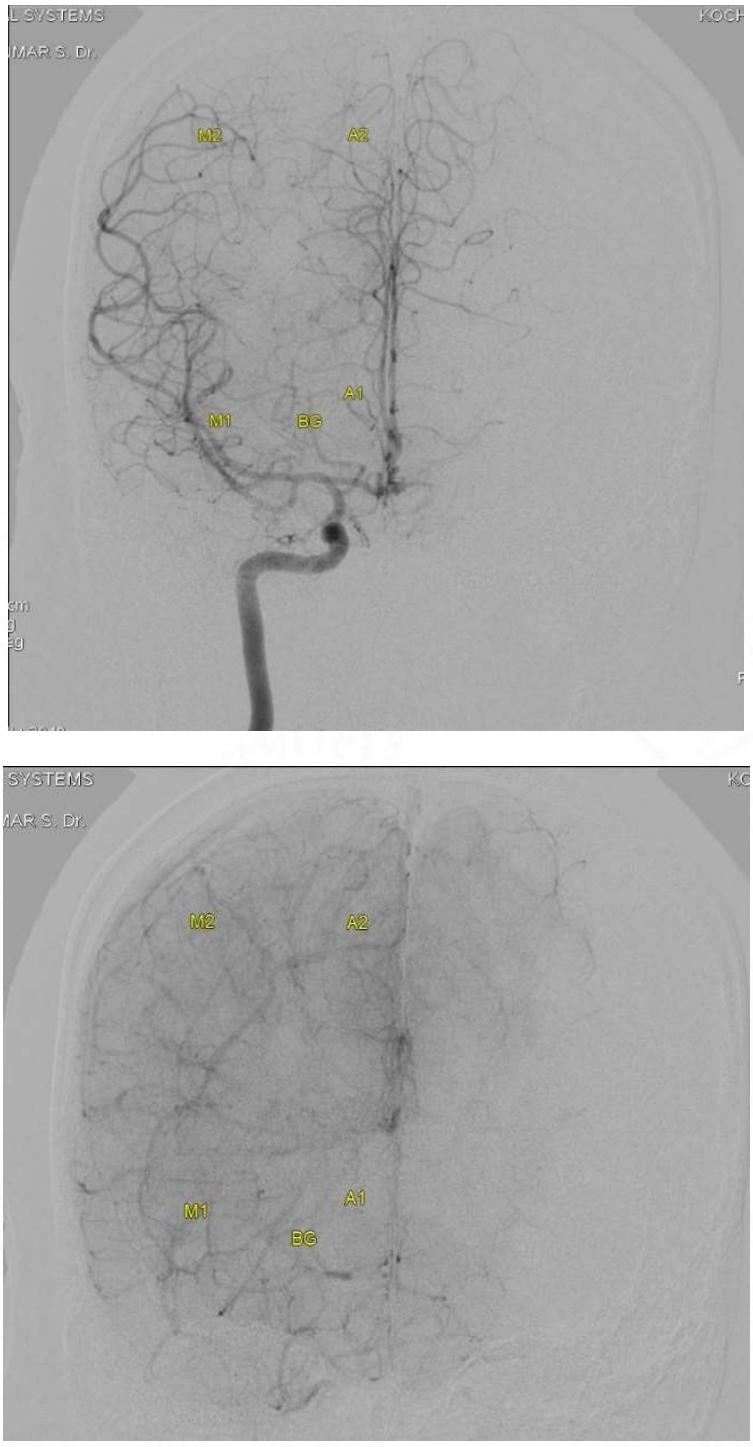

Figure 5: Regions used for grading collaterals on DSA – depicting BG, M1, M2, A1, A2 regions – On ICA injection in arterial phase (above pane) and capillary phase (below pane).

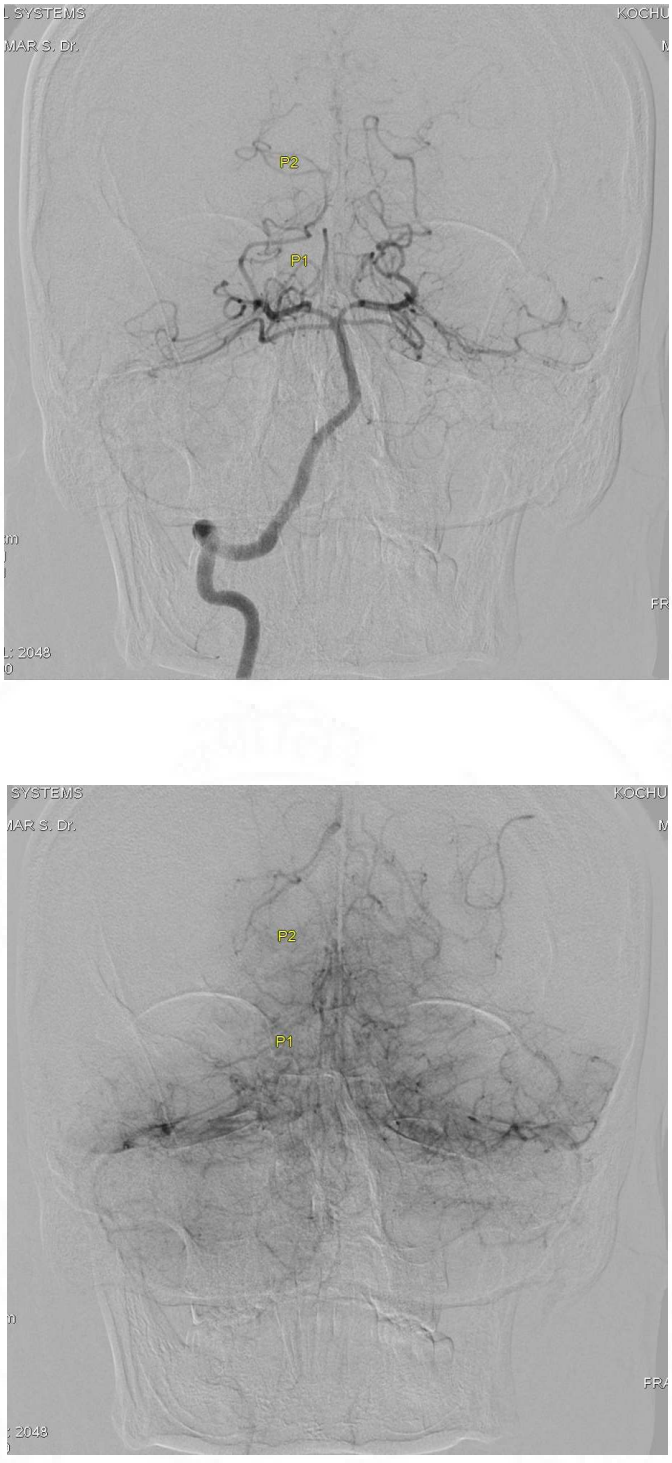

Figure 6 - Regions used for grading collaterals on DSA – depicting P1 and P2 regions – On VA injection in arterial phase (above pane) and in capillary phase (below pane)

Collaterals were graded on DSA at each region using the following grading system shown in Table 2 and figure 7-10. The perfusion deficit is assessed by the capillary blush.

Table 2: Collateral grading system on DSA

Grade 0	No collaterals visible (absence of any capillary blush) with perfusion deficit
Grade 1	Mild to moderate collaterals with some perfusion deficit
Grade 2	Extensive collaterals with no perfusion deficit
Grade 3	Normal antegrade flow with no collaterals or perfusion deficit

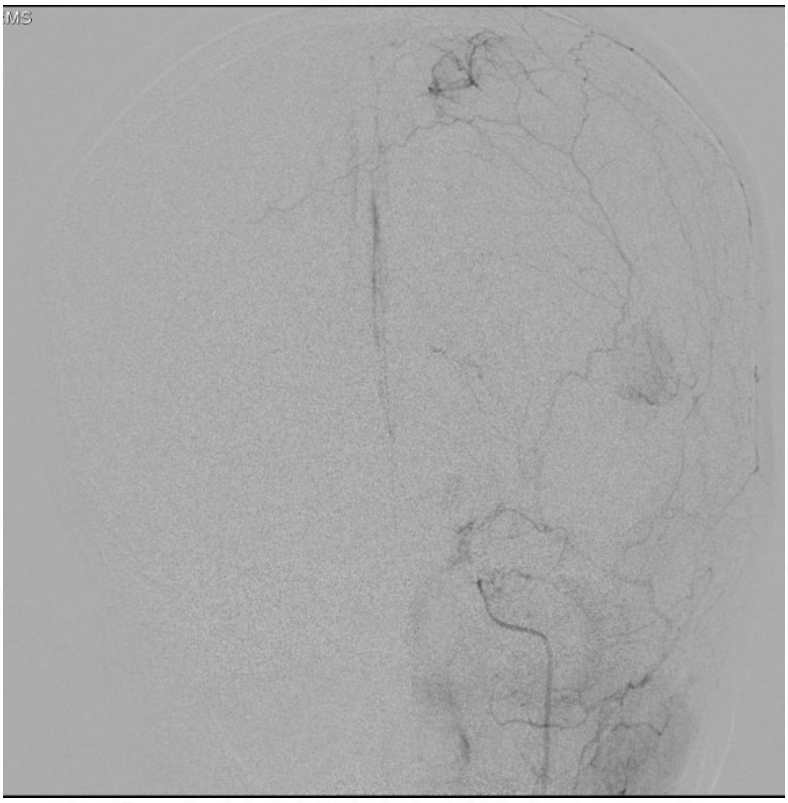

Figure 7: Grade 0 perfusion on DSA in left M1 region – no visible collaterals with large perfusion deficit

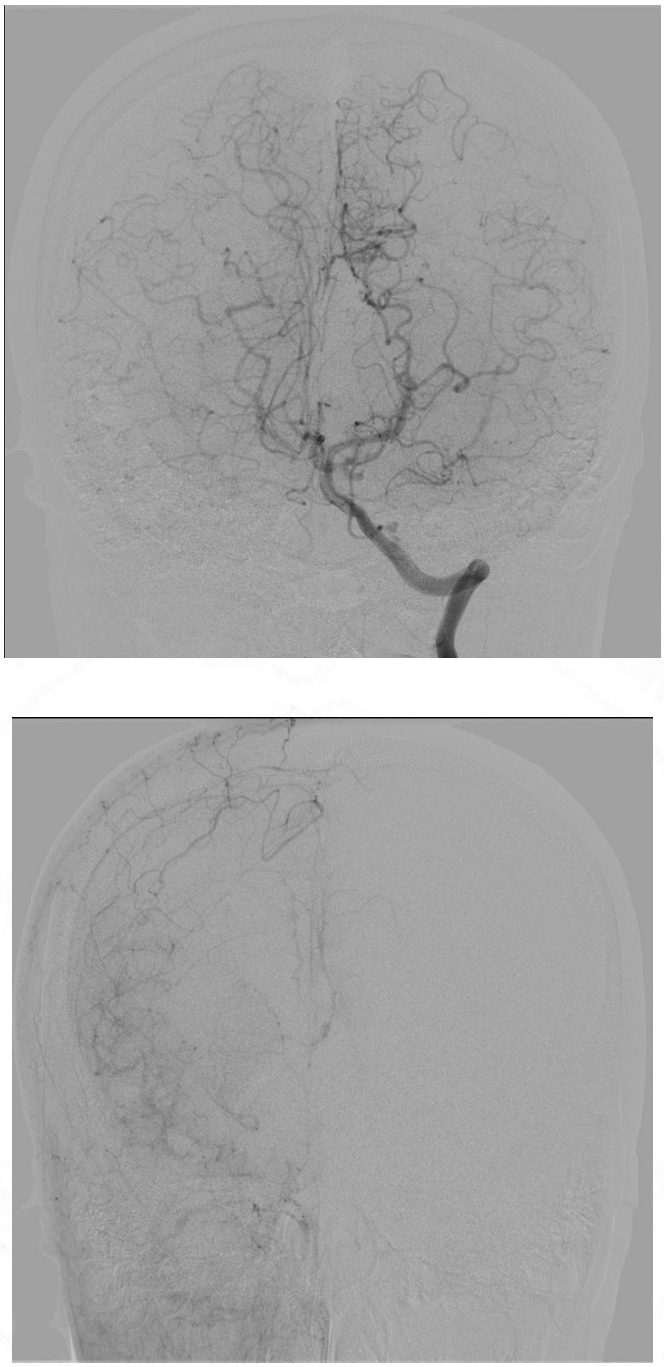

Figure 8: Grade 1 collaterals on DSA in right M1 region – above panel shows collaterals in the M1 region during the arterial phase and below panel shows a perfusion deficit in the same region during capillary phase.

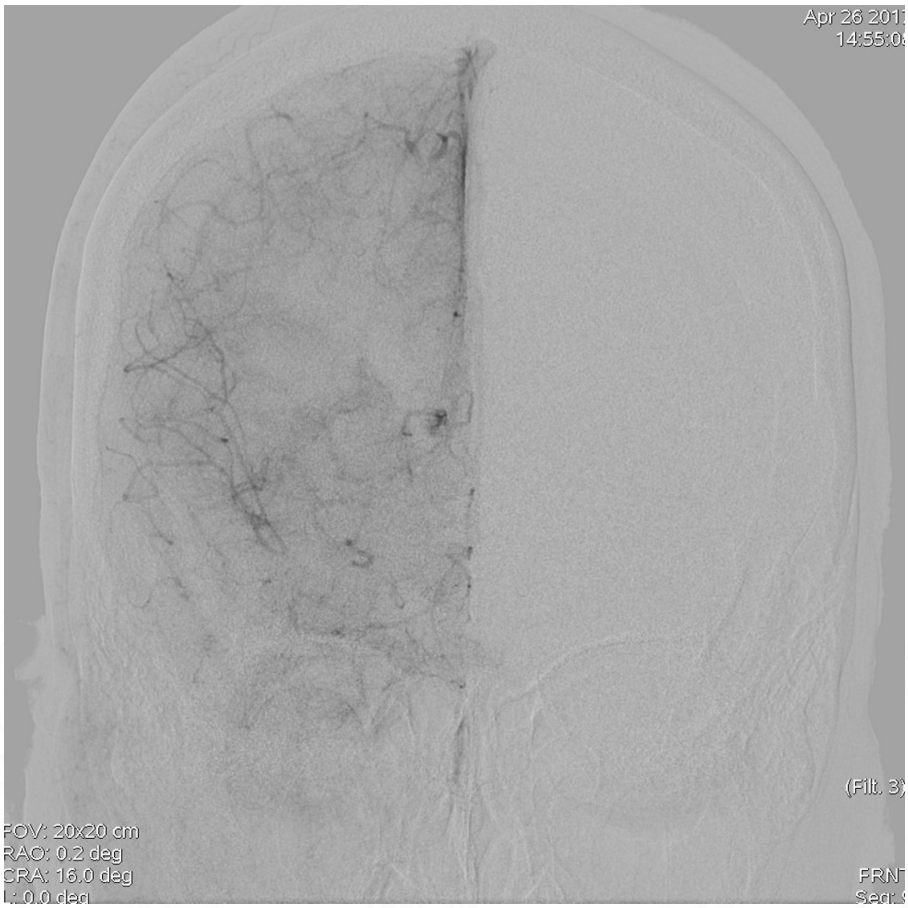

Figure 9: Grade 2 collaterals on DSA at M1 region – well-formed pial-pial collaterals can be seen originating from ACA with no perfusion deficit.

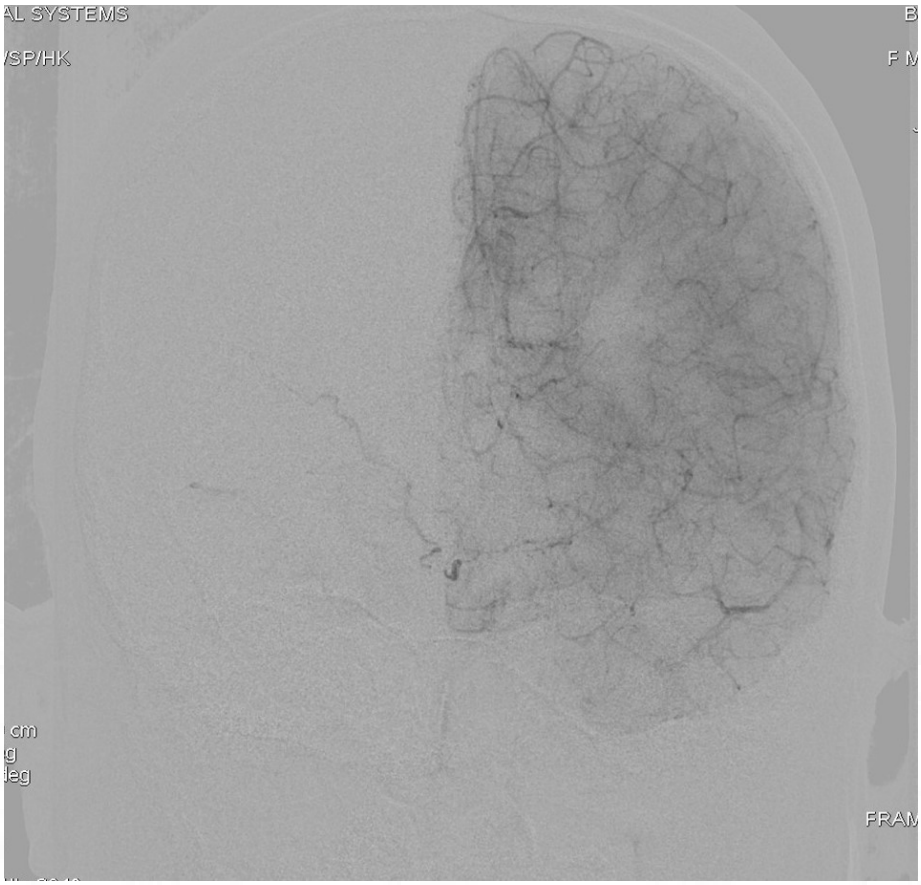

Figure 10: Grade 3 collaterals on DSA in the left M1 region – there is very good capillary blush without any evidence for collaterals

Collaterals were graded on ASL at each region (except basal ganglia) using the following grading system shown in Table 3 and figure 11-14.

Table 3: Collateral grading system on ASL

Grade 0	No or minimal ASL signal
Grade 1	Moderate ASL signal with arterial transit artefact (ATA)
Grade 2	High signal with ATA
Grade 3	Normal perfusion without ATA

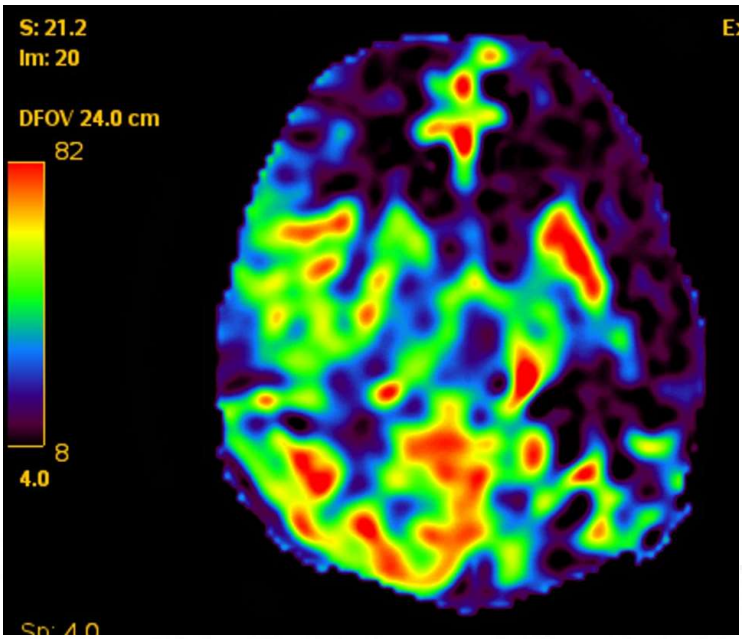

Figure 11: Grade 0 perfusion on ASL in the left M1 region – There is absent ASL signal in the left insular region

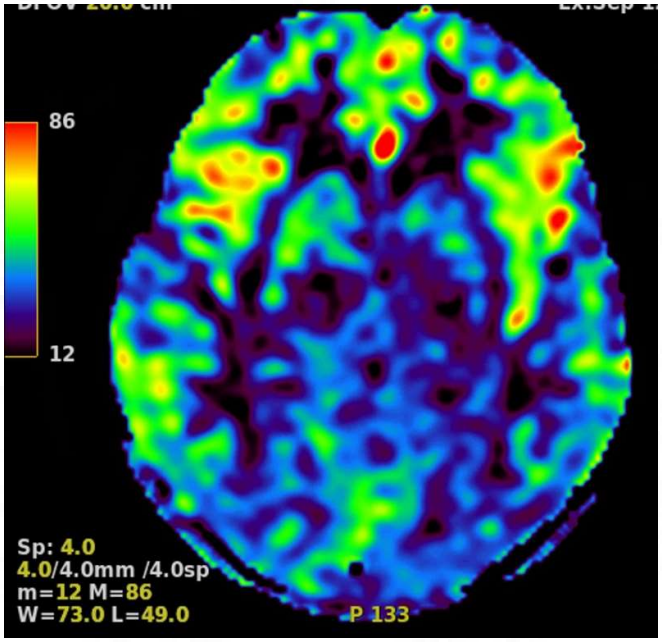

Figure 12: Grade 1 collaterals on ASL in right M1 region – Moderate ASL signal with ATA seen in right insula.

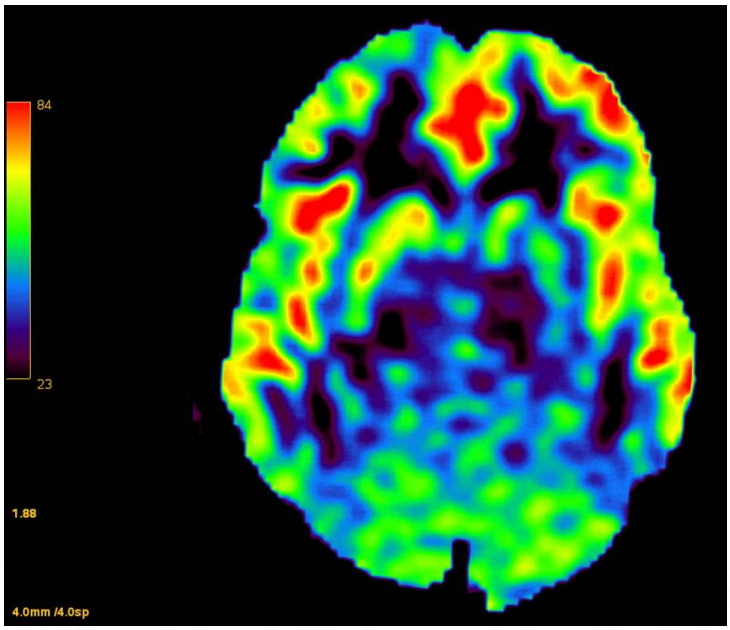

Figure 13: Grade 2 collaterals on ASL in right M1 region – Very good ASL signal with ATA is seen in right insula

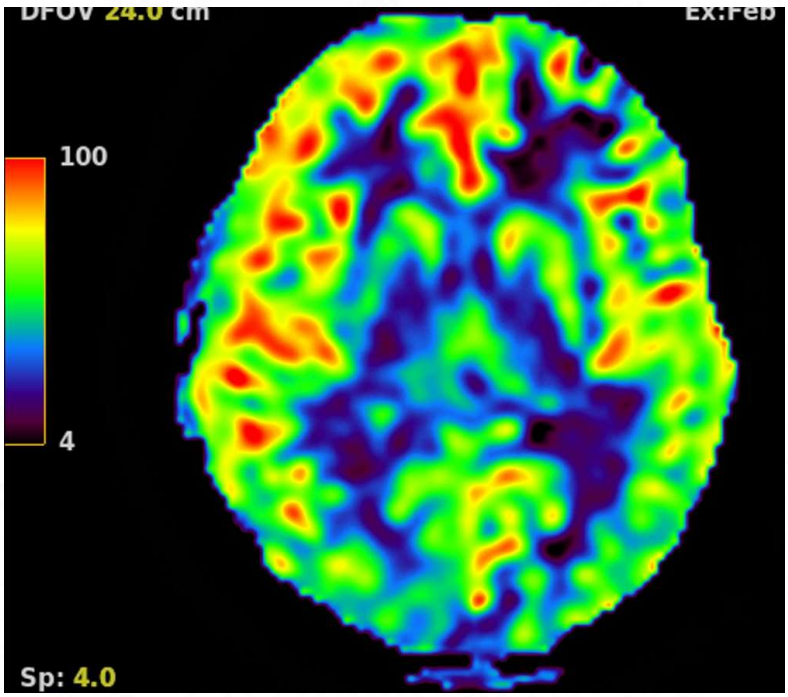

Figure 14: Grade 3 collaterals on ASL in the right M1 region – Normal ASL signal intensity without ATA in right insula.

For grading the collaterals at the basal ganglia using ASL, only 3 grades were used because of difficulty in analysing ATA in this region as shown in Table 4.

Table 4: Collateral grading at basal ganglia on ASL

Grade 0	No or minimal ASL signal
Grade 1	Mild to Moderate ASL signal
Grade 2	High ASL signal

The quantitative analysis was done by calculating ASL signal intensity ratio (ASL-SIR) by placing regions of interest (ROIs) of area 7-15mm^2 on ASL source images in the above said 7 regions in each hemisphere. ASL signal intensity ratio (SIR) is derived with the numerator as the signal intensity from the ROI, and the denominator as the signal intensity from a similar sized ROI in a normally perfused cortical area of the ipsilateral cerebellum (figure 15).

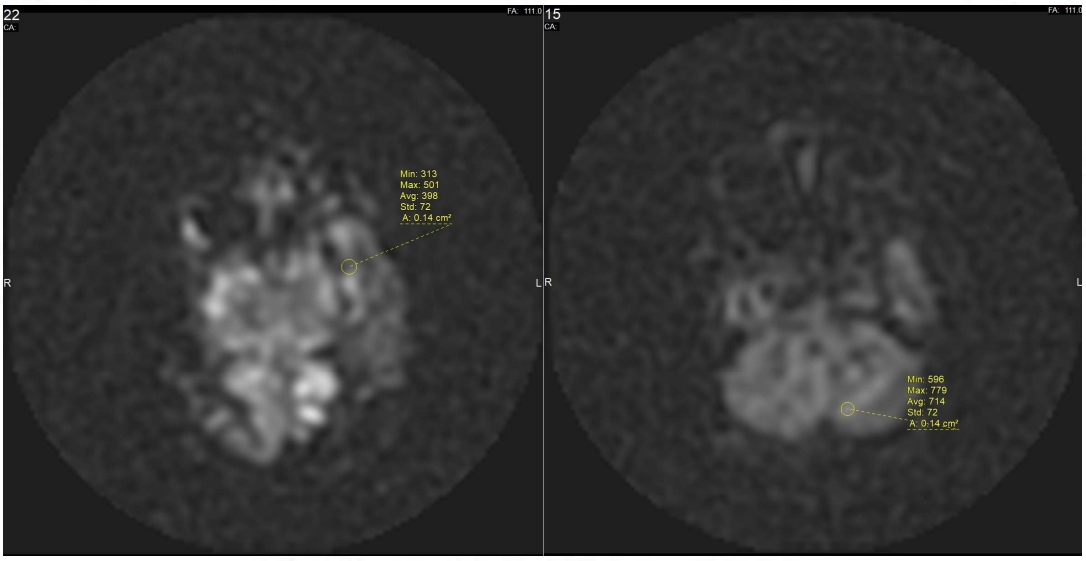

Figure 15: Calculation of ASL-SIR: ASL signal intensity calculated from left insula (right panel) and left cerebellum (left panel)

Statistical analysis:

Categorical variables were summarized as numbers and percentages. Continuous variables were summarized using mean +/- standard deviation and median. When there was non-normal distribution of data, non-parametric tests were used. Normally distributed quantitative data was analyzed with the independent t test. Qualitative variables were compared with the Chi-square test. When any cell had a count of less than 5, Fisher's exact test was used. The correlation between ASL and DSA collateral assessments was quantified using kappa values. Interpretation of Kappa values is as shown in table-5.

The data was collected and tabulated using a Microsoft EXCEL spreadsheet. Final statistical analysis was done using Jamovi 2.3.26 software. A p -value < 0.05 was considered statistically significant.

Table 5: Interpretation of Kappa values

Kappa value	Strength of agreement
< 0.20	Poor
0.21 - 0.40	Fair
0.41 - 0.60	Moderate
0.61 - 0.80	Good
0.81 - 1.00	Very good

RESULTS

Total number of patients = 46

Demographics and clinical characteristics

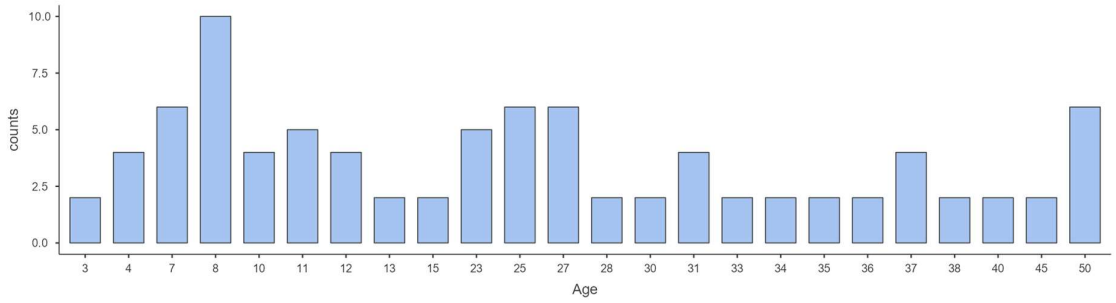

Figure 16: Frequency distribution of patient's according to age

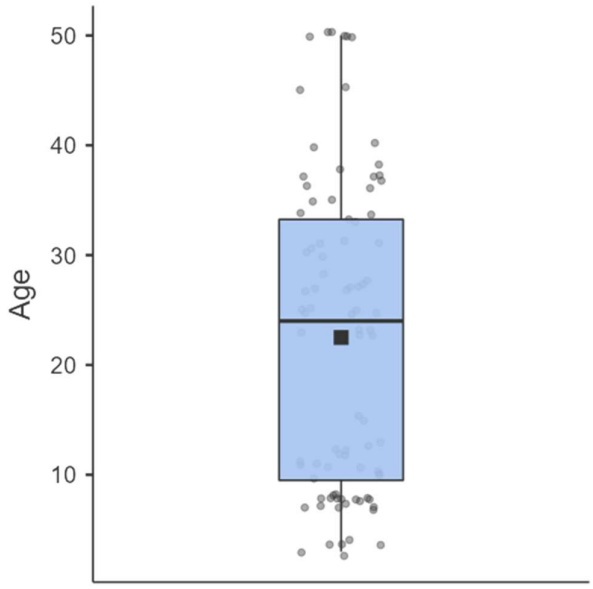

Figure 17: Forrest plot of age distribution

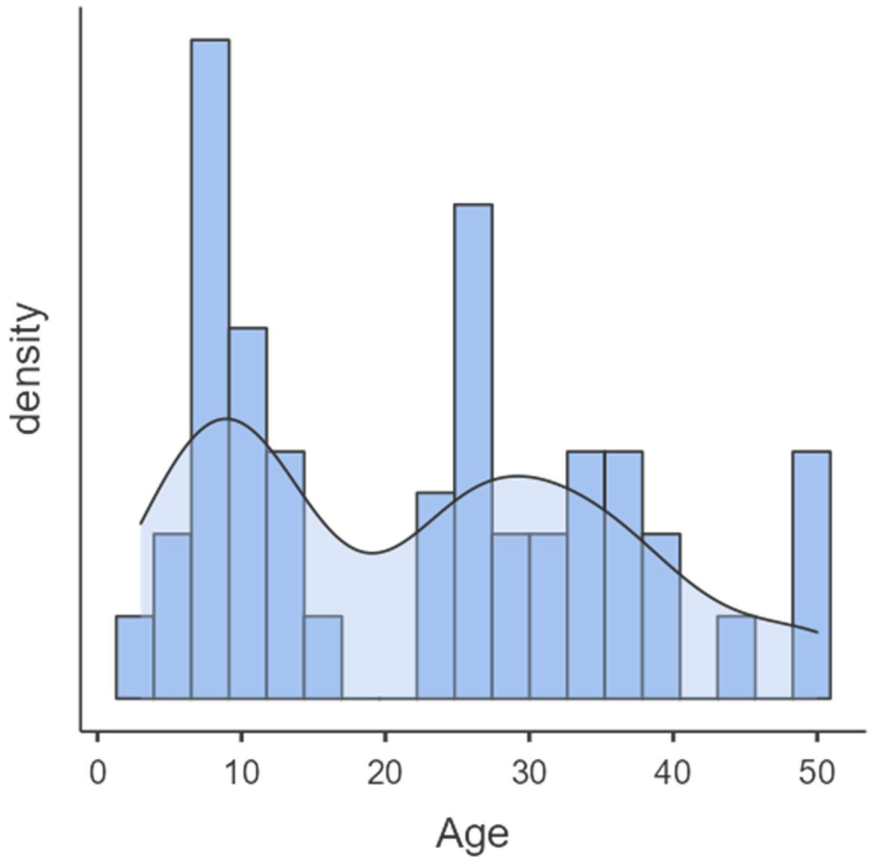

Figure 18: Plot depicting bimodal distribution of age

Table 6: Age descriptives

	Age
Mean Age	22.5 years
Median	24 years
Standard deviation	14
Minimum age	3 years
Maximum age	50 years

The mean age of presentation is 22.5 years, while median age of presentation is 24 years and standard deviation of age is 22.5 +/- 14 years. The age range is between 3 and 50 years. There is bimodal distribution with one peak in 1st decade and 2nd peak in 3rd and 4th decade.

Table 7: Gender distribution

Gender	N (%)
Males	22 (47.8%)
Females	24 (52.2%)

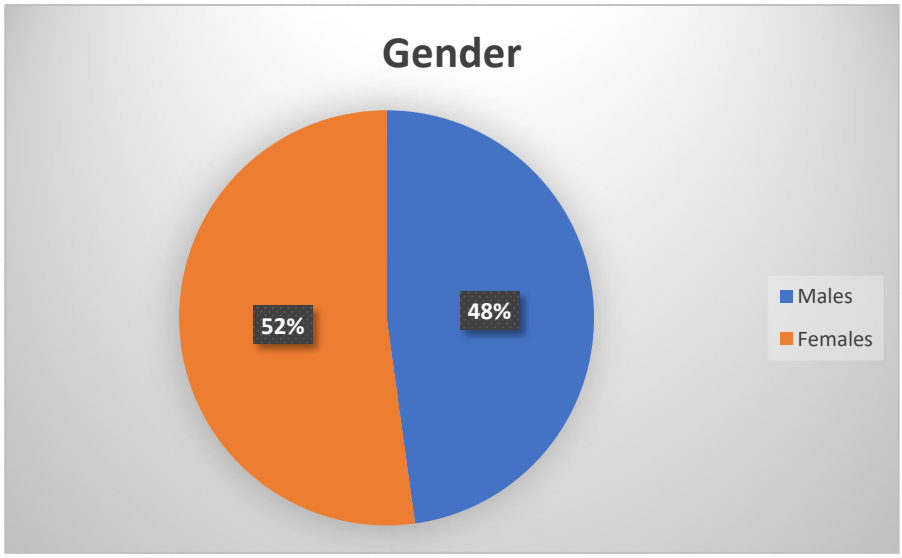

Figure 19: Gender distribution

Out of the 46 patients 22 were male (47.8%) and remaining 24 were female (52.2%).

Table 8: Frequency distribution of various clinical symptoms

Symptom	N	%
Weakness	30	65.2%
Seizure	11	23.9%
Headache	9	19.6%
Paresthesia	7	15.2%
Vertigo	3	6.5%
Behavioural change	2	4.3%
Ataxia	1	2.2%

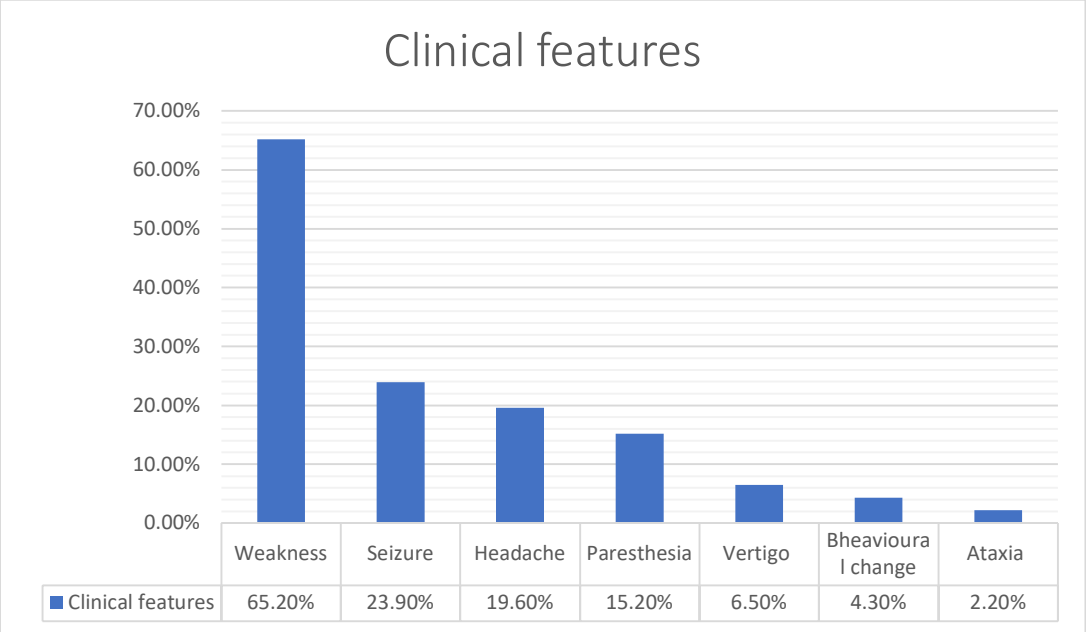

Figure 20: Frequency distribution of clinical symptoms

Of the 46 patients, 65.2% patients had weakness, 23.9% had seizures, 19.6% had headache, 15.2% had paresthesias, 6.5% had vertigo, 4.3% had behavioural change and 2.2% had ataxia.

Table 9: Frequency distribution of type of presentation – ischemic vs hemorrhagic

	N (%)
Ischemic	40 (89.1%)
Hemorrhagic	5 (10.9%)
TIA	22 (47.8%)

Of the 46 patients, 40 of them had ischemic presentation (either TIA or an ischemic stroke) and 5 patients had hemorrhagic presentation (parenchymal bleed or SAH). 22 of the 46 patients had history of TIA. 1 patient was detected to have MMD while he was evaluated for headache.

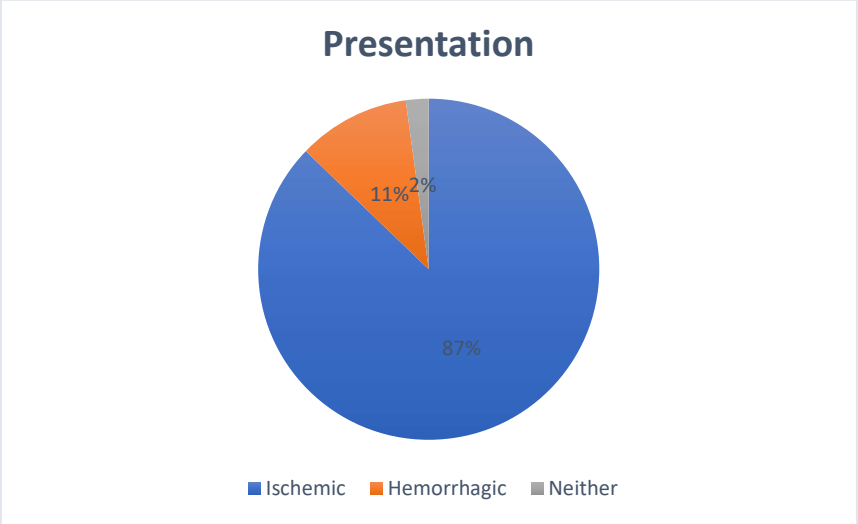

Figure 21: Type of presentation – ischemic vs hemorrhagic

Out of the 92 hemispheres from the 46 patients, 4 hemispheres were excluded as the patient underwent revascularisation in the corresponding hemisphere. Of the remaining 88 hemispheres included for the study, 7 were normal on angiography.

Of the 45 patients with either ischemic or hemorrhagic presentation, 28 were symptomatic unilaterally (14 on left side and 14 on right side), while 17 were symptomatic bilaterally.

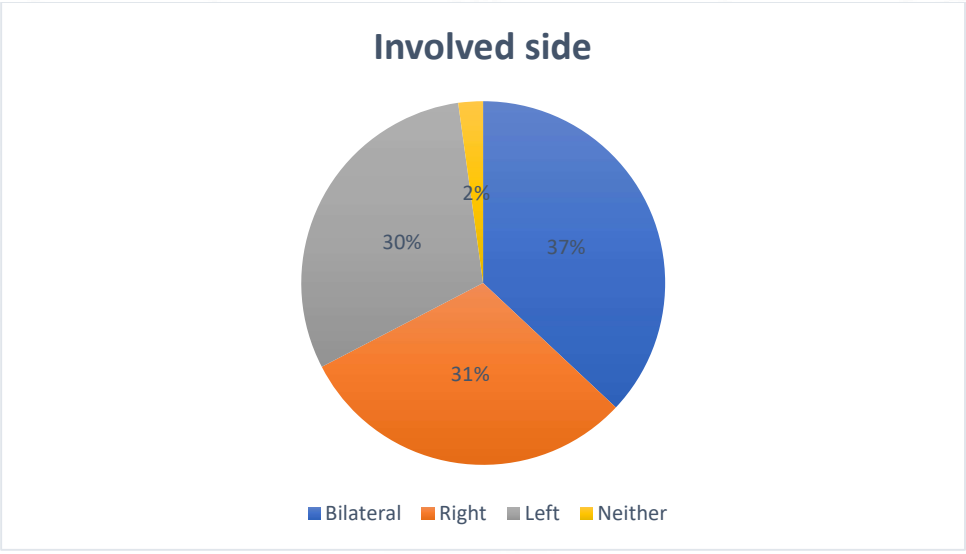

Figure 22: Symptomatically involved side

Table 10: Symptomatically involved side

Symptomatic side	N (%)
Bilateral	17 (37%)
Right side	14 (30.4%)
Left side	14 (30.4%)
Neither	1 (2.2%)

Admission NIHSS scores

The mean NIHSS score is 1 with a standard deviation of 2.3 with minimum being 0 and while maximum was 13.

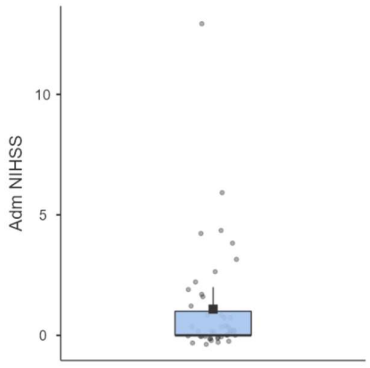

Figure 23: Forrest plot distribution of the NIHSS score

Table 11: Frequency distribution of admission mRS scores

mRS score	N (%)
0	23 (50%)
1	10 (21.7%)
2	9 (19.6%)
3	3 (6.5%)
4	1 (2.2%)

Admission mRS score

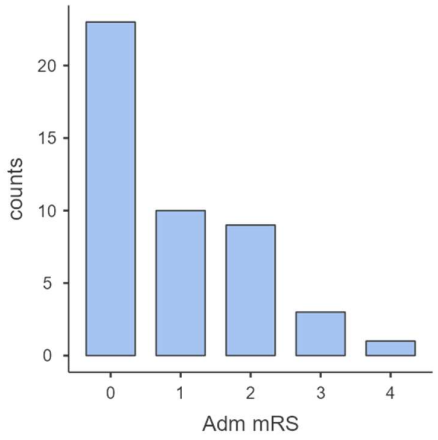

Figure 24: Frequency distribution of admission mRS scores

Interval between the DSA and MR-ASL scans

The mean interval between DSA and MR-ASL was 21.1 days with a standard deviation of 26.9 days. [minimum duration was 1 day and maximum was 88 days]

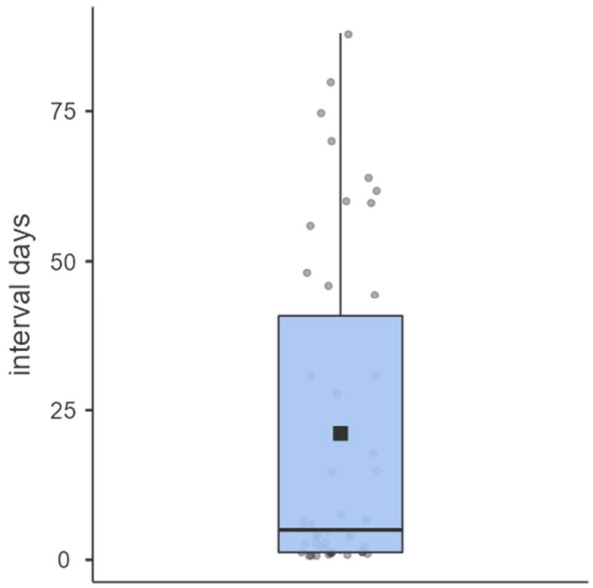

Figure 25: Forrest plot of distribution of time interval between DSA and MR-ASL scans

DSA findings

The Suzuki staging of the 88 hemispheres is described in the following table and diagrams.

Table 12: Frequency of various Suzuki grades in total 88 hemisphere

Suzuki stage	N	%
0	7	8%
1	10	11.4%
2	13	14.8%
3	24	27.3%
4	29	33%
5	5	5.7%

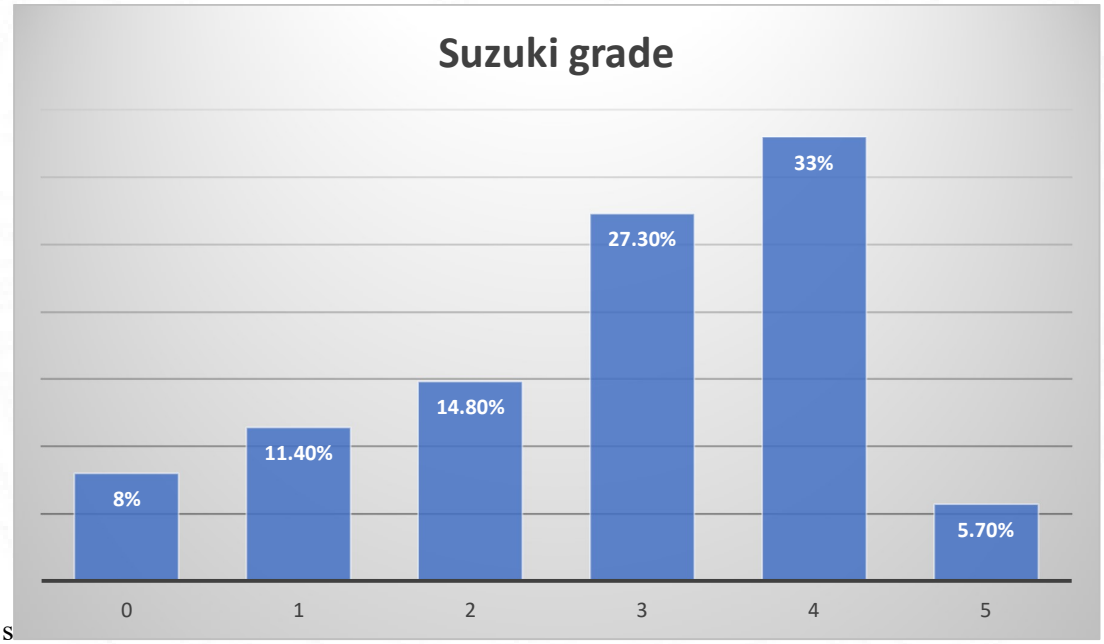

Figure 26: Frequency of various Suzuki stages in total 88 hemispheres

DSA collateral scoring in all the regions of interest

Table 13: Frequency distribution of various grades of collaterals on DSA in basal ganglia region

DSA collateral grade	N (%)
1	44 (50%)
2	30 (34.1%)
3	14 (15.9%)

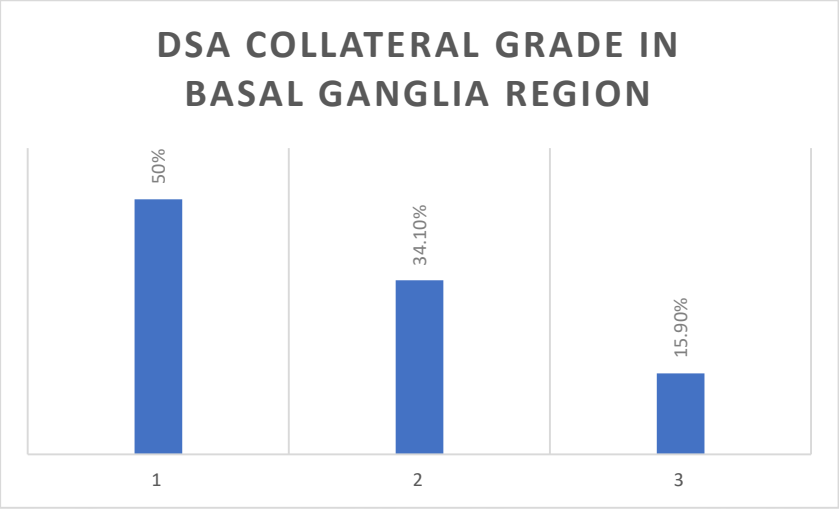

Figure 27: Frequency distribution of various grades of collaterals on DSA in basal ganglia region

Table 14: Frequency distribution of various grades of collaterals on DSA in M1 region

DSA collateral grade	N (%)
0	1 (2.2%)
1	42 (47.7%)
2	28 (31.8%)
3	17 (19.3%)

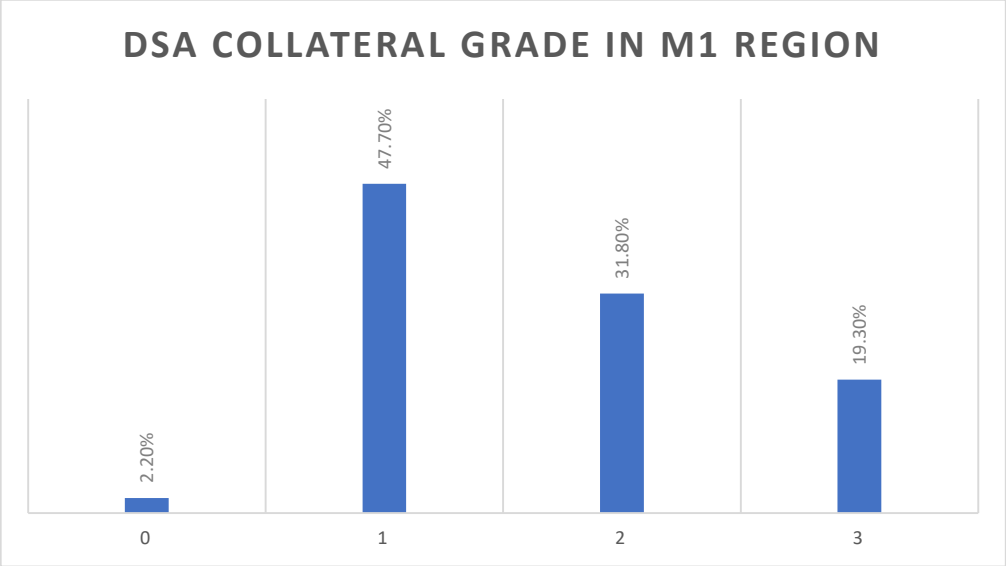

Figure 28: Frequency distribution of various grades of collaterals on DSA in M1 region

Table 15: Frequency distribution of various grades of collaterals on DSA in M2 region

DSA collateral grade	N (%)
0	4 (4.5%)
1	54 (61.4%)
2	14 (15.9%)
3	16 (18.2%)

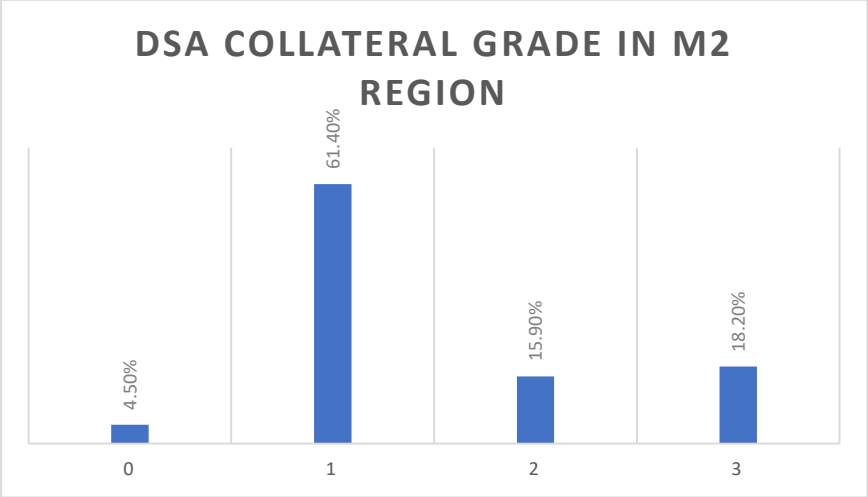

Figure 29: Frequency distribution of various grades of collaterals on DSA in M2 region

Table 16: Frequency distribution of various grades of collaterals on DSA in A1 region

DSA collateral grade	N (%)
0	0
1	42 (47.7%)
2	27 (30.7%)
3	19 (21.6%)

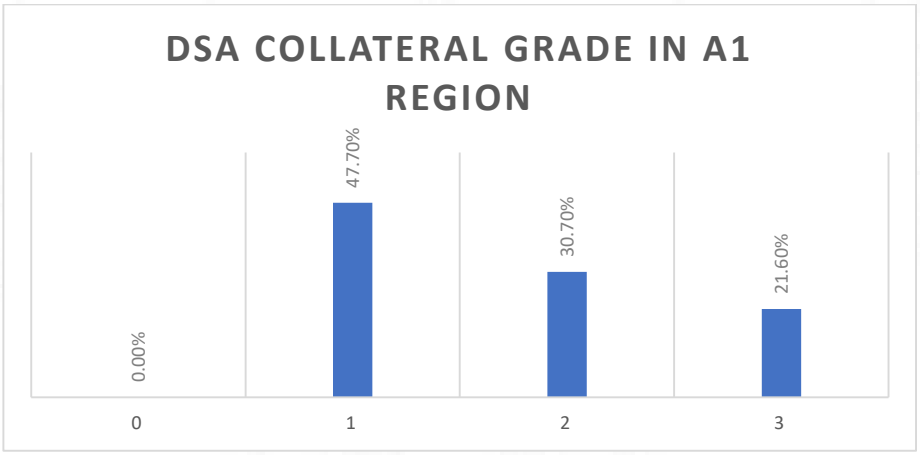

Figure 30: Frequency distribution of various grades of collaterals on DSA in A1 region

Table 17: Frequency distribution of various grades of collaterals on DSA in A2 region

DSA collateral grade	N (%)
0	0
1	39 (44.3%)
2	27 (30.7%)
3	22 (25%)

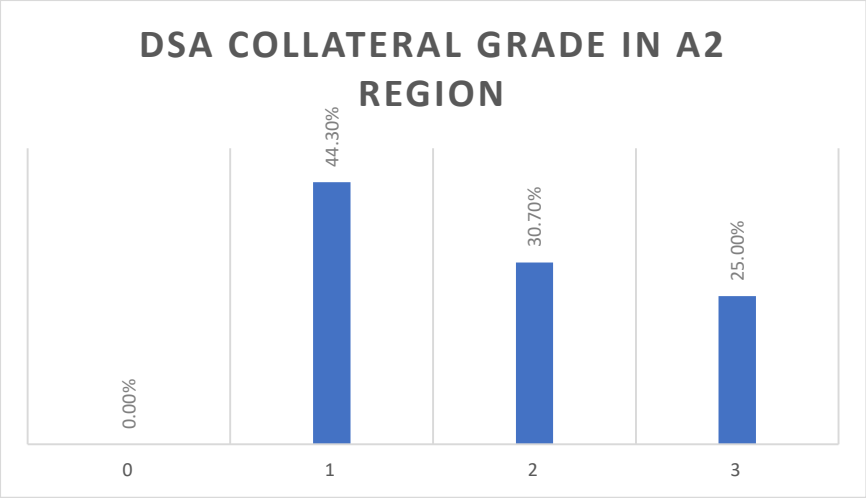

Figure 31: Frequency distribution of various grades of collaterals on DSA in A2 region

Table 18: Frequency distribution of various grades of collaterals on DSA in P1 region

DSA collateral grade	N (%)
0	0
1	13 (14.8%)
2	9 (10.2%)
3	66 (75%)

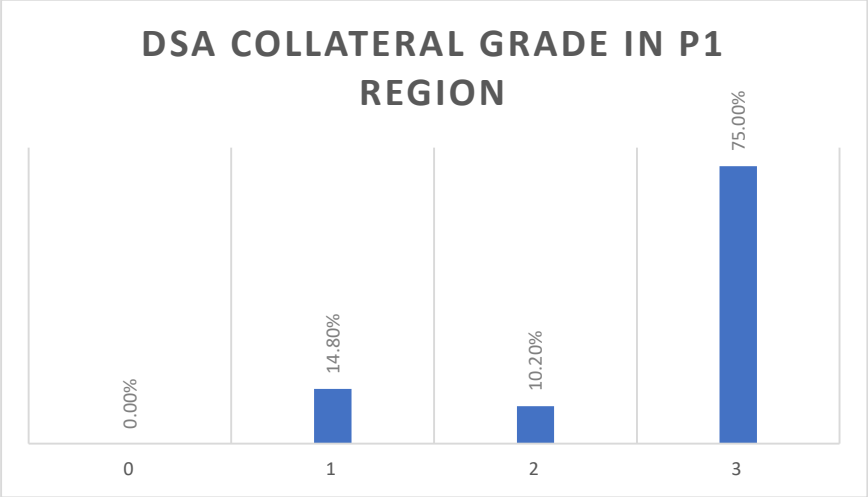

Figure 32: Frequency distribution of various grades of collaterals on DSA in P1 region

Table 19: Frequency distribution of various grades of collaterals on DSA in P2 region

DSA collateral grade	N (%)
0	1 (1.1%)
1	19 (21.6%)
2	2 (2.3%)
3	66 (75%)

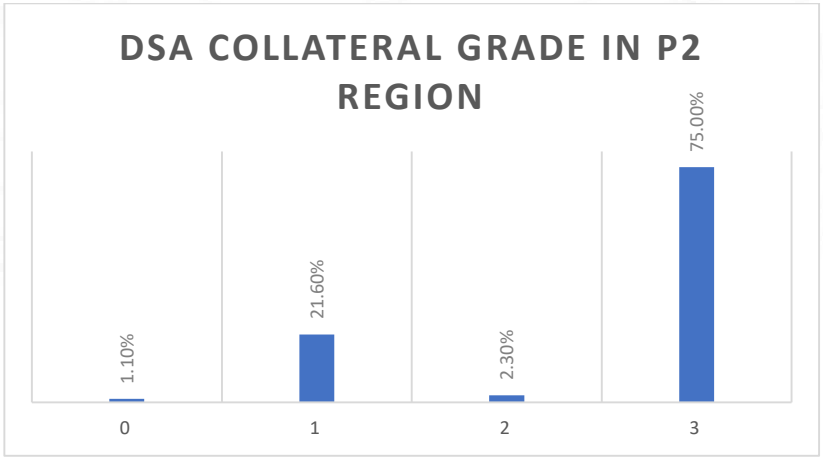

Figure 33: Frequency distribution of various grades of collaterals on DSA in P2 region

At various Suzuki grades, the degree of collaterals graded on DSA were compared at each ROI to look for change in collateral status on DSA with the DSA Suzuki stage. This is done to predict the collateral shift with increasing severity of the MMD. On chi-square test this change in collateral grading with Suzuki staging is statistically significant at all the ROIs ($p<0.001$).

Table 20: DSA collateral grading at basal ganglia across various Suzuki grades

	DSA collateral grading at basal ganglia			
Suzuki grading	1	2	3	Total
0	0	0	7	7
1	4	0	6	10
2	5	7	1	13
3	8	16	0	24
4	23	5	0	29
5	4	1	0	5
Total	44	30	14	88

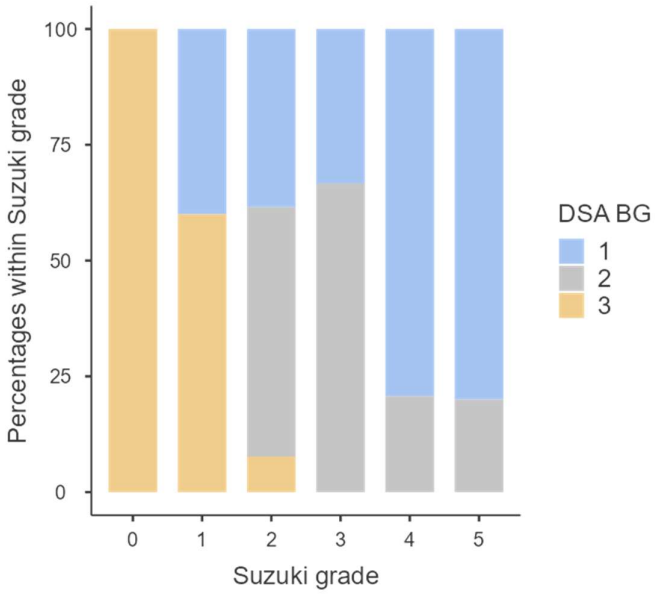

Figure 34: DSA collateral grading at basal ganglia across various Suzuki grades

Table 21: DSA collateral grading at M1 region across various Suzuki grades

	DSA collateral grading at M1 region				
Suzuki grading	0	1	2	3	Total
0	0	0	0	7	7
1	0	1	2	7	10
2	0	1	9	3	13
3	0	13	11	0	24
4	1	23	5	0	29
5	0	4	1	0	5
Total	1	42	28	17	88

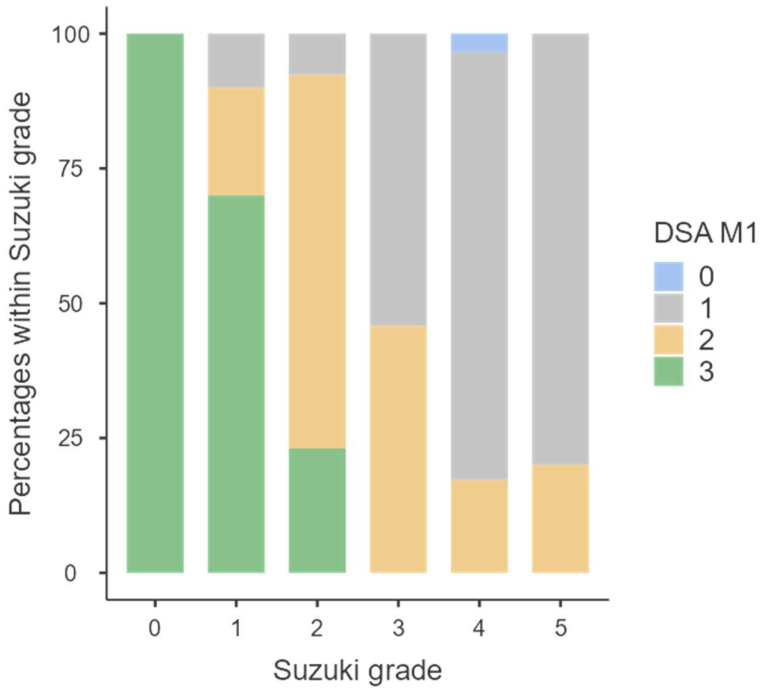

Figure 35: DSA collateral grading at M1 region across various Suzuki grades

Table 22: DSA collateral grading at M2 region across various Suzuki grades

	DSA collateral grading at M2 region				
Suzuki grading	0	1	2	3	Total
0	0	0	0	7	7
1	0	2	1	7	10
2	0	8	3	2	13
3	1	16	7	0	24
4	3	26	0	0	29
5	0	2	3	0	5
Total	4	54	14	16	88

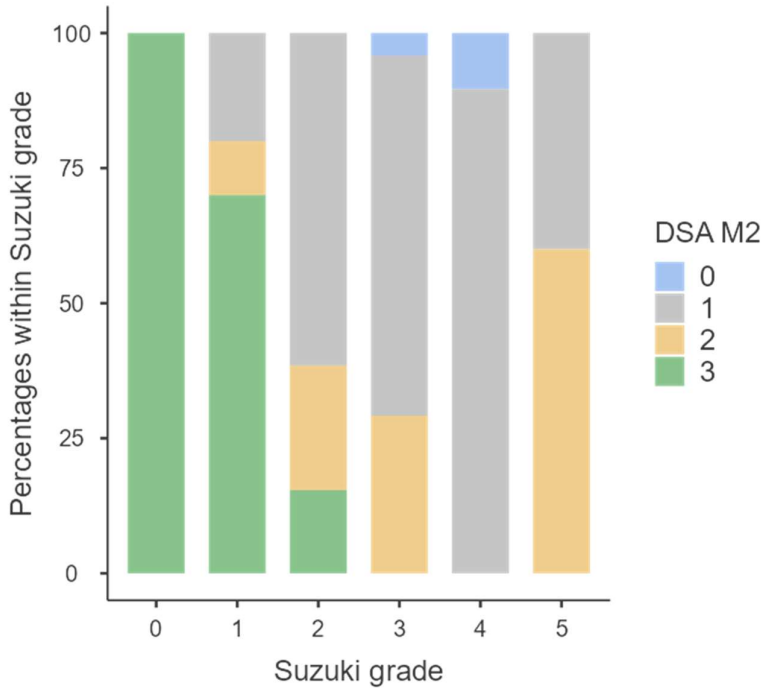

Figure 36: DSA collateral grading at M2 region across various Suzuki grades

Table 23: DSA collateral grading at A1 region across various Suzuki grades

	DSA collateral grading at A1 region			
Suzuki grading	1	2	3	Total
0	0	0	7	7
1	2	3	5	10
2	3	8	2	13
3	11	10	3	24
4	23	4	2	29
5	4	2	0	5
Total	42	27	19	88

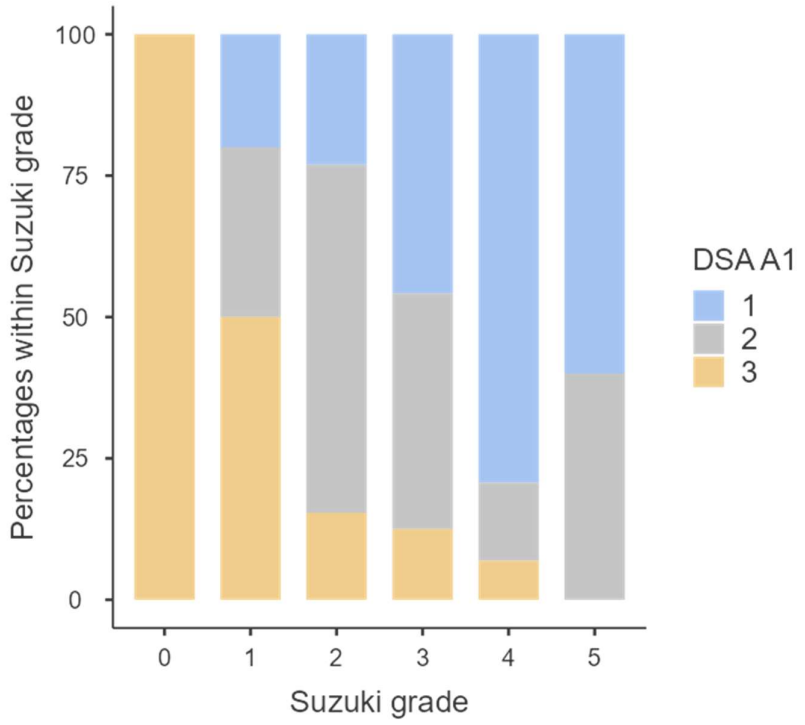

Figure 37: DSA collateral grading at A1 region across various Suzuki grades

Table 24: DSA collateral grading at A2 region across various Suzuki grades

	DSA collateral grading at A2 region			
Suzuki grading	1	2	3	Total
0	0	0	7	7
1	2	2	6	10
2	2	7	4	13
3	9	12	3	24
4	24	3	2	29
5	2	3	0	5
Total	39	27	22	88

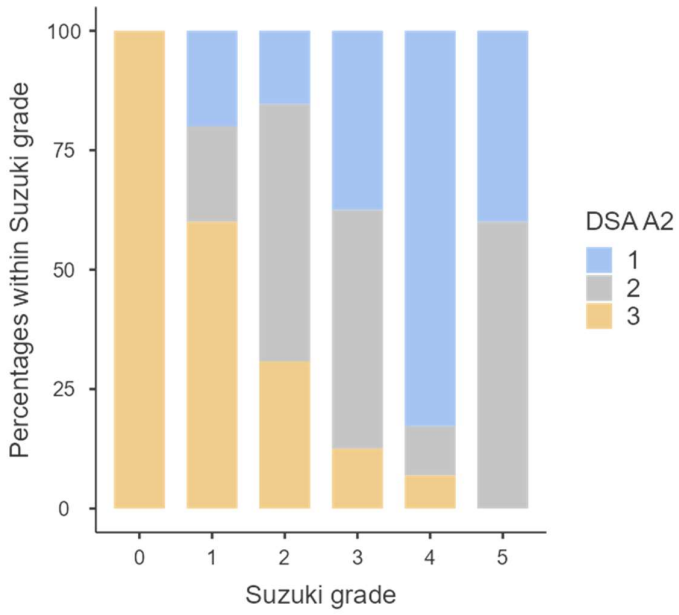

Figure 38: DSA collateral grading at A2 region across various Suzuki grades

Table 25: DSA collateral grading at P1 region across various Suzuki grades

	DSA collateral grading at P1 region			
Suzuki grading	1	2	3	Total
0	0	0	7	7
1	0	1	9	10
2	0	0	13	13
3	0	3	21	24
4	12	5	12	29
5	1	0	4	5
Total	13	9	66	88

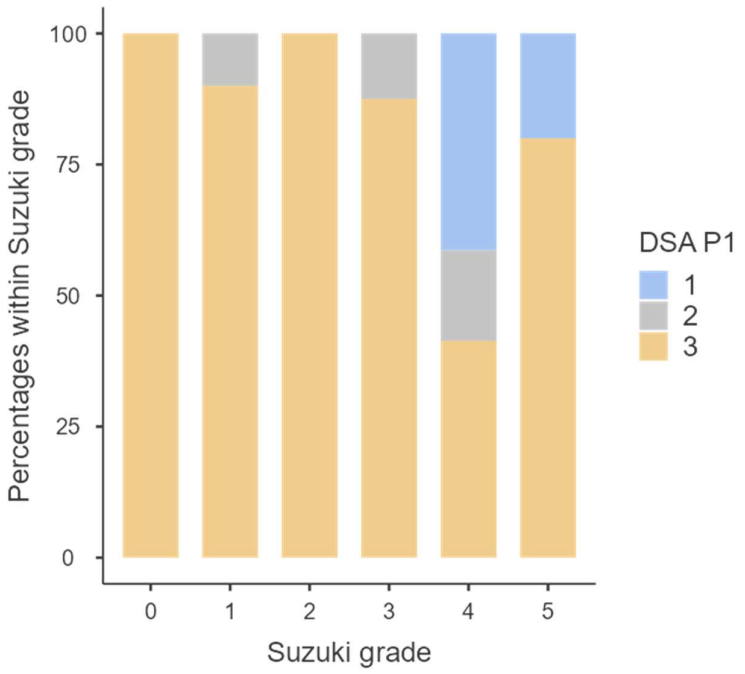

Figure 39: DSA collateral grading at P1 region across various Suzuki grades

Table 26: DSA collateral grading at P2 region across various Suzuki grades

	DSA collateral grading at P2 region				
Suzuki grading	0	1	2	3	Total
0	0	0	0	7	7
1	0	0	1	9	10
2	0	0	0	13	13
3	0	3	0	21	24
4	1	16	0	12	29
5	0	0	1	4	5
Total	1	19	2	66	88

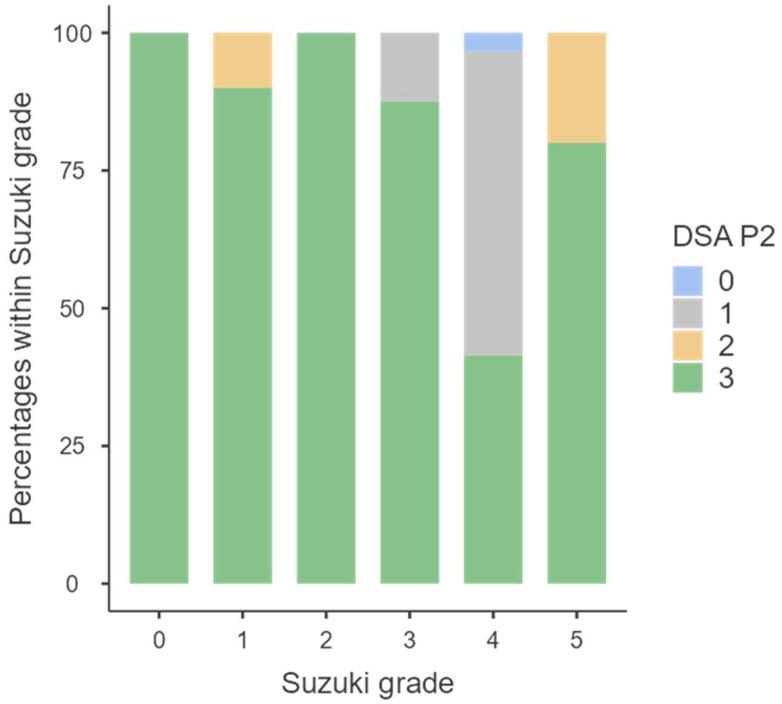

Figure 40: DSA collateral grading at P2 region across various Suzuki grades

ASL signal intensity ratio

Table 27: ASL signal intensity ratio at various ROIs

ASL SIR	Mean ± SD	Median	Range
BG	0.97 ± 0.2	0.96	0.56-1.5
M1	0.94 ± 0.27	0.96	0.26-1.73
M2	0.78 ± 0.31	0.74	0.18-1.5
A1	0.91 ± 0.27	0.94	0.36-1.6
A2	0.94 ± 0.27	0.95	0.36-1.6
P1	1.1 ± 0.24	1.12	0.3-1.7
P2	1.07 ± 0.27	1.14	0.2-1.6

Table 28: Correlation between Suzuki stage and ASL SIR at various ROIs

	χ^2	p value
BG	8.39	0.136
M1	26	<0.001
M2	27	<0.001
A1	14.1	0.015
A2	21.6	<0.001
P1	6.49	0.262
P2	16	0.007

On non-parametric One-way ANNOVA (Kruskal-Wallis) test, when Suzuki stage was compared with ASL signal intensity ratio at various ROIs, it has shown statistically significant correlation in the M1, M2, A1, A2 and P2 regions, while it did not show correlation in the remaining ROIs (BG and P1). (Table 27)

Correlation between DSA collaterals and the ASL-SIR at various ROIs

On One-way ANNOVA (Kruskal-Wallis) test, the DSA collaterals grade was compared to the ASL-SIR at each ROI to look whether ASL-SIR can be used to predict the different grades of collaterals. The ASL-SIR could predict the collateral grade on DSA across all the ROIs ($p<0.001$).

Table 29: Correlation between DSA collateral grade and ASL SIR at various ROIs

	χ^2	p value
BG	18.1	<0.001
M1	43.2	<0.001
M2	41.1	<0.001
A1	41.1	<0.001
A2	49.1	<0.001
P1	12.4	0.002
P2	39.9	<0.001

When pair wise comparisons were done using Dwass-Steel-Critchlow-Fligner test in One-way ANNOVA, the difference was more obvious between collateral grades 0 and 1, 0 and 2, 1 and 2. But these values cannot be used to differentiate between grades 2 and 3 of collaterals on DSA.

Table 30: Pairwise comparisons at BG between DSA collateral grades using ASL-SIR

		W	P
1	2	5.57	< .001
1	3	3.36	0.046
2	3	-2.43	0.198

Table 31: Pairwise comparisons at M1 between DSA collateral grades using ASL-SIR

		W	P
0	1	2.39	0.331
0	2	2.37	0.337
0	3	2.29	0.367
1	2	7.65	< .001
1	3	7.06	< .001
2	3	2.12	0.438

Table 32: Pairwise comparisons at M2 between DSA collateral grades using ASL-SIR

		W	P
0	1	4.66	0.006
0	2	4.22	0.015
0	3	4.21	0.016
1	2	5.12	0.002
1	3	7.41	< .001
2	3	1.11	0.862

Table 33: Pairwise comparisons at A1 between DSA collateral grades using ASL-SIR

		W	P
1	2	7.34	< .001
1	3	7.30	< .001
2	3	2.55	0.169

Table 34: Pairwise comparisons at A2 between DSA collateral grades using ASL-SIR

		W	P
1	2	8.48	< .001
1	3	7.89	< .001
2	3	1.35	0.605

Table 35: Pairwise comparisons at P1 between DSA collateral grades using ASL-SIR

		W	P
1	2	3.584	0.030
1	3	4.860	0.002
2	3	-0.909	0.797

Table 36: Pairwise comparisons at P2 between DSA collateral grades using ASL-SIR

		W	p
0	1	2.31	0.360
0	2	1.73	0.611
0	3	2.41	0.322
1	2	3.18	0.110
1	3	8.64	< .001
2	3	-1.15	0.850

ASL collateral scoring in all the regions of interest

Table 37: Frequency distribution of various grades of collaterals on ASL in basal ganglia region

ASL collateral grade	N (%)
0	0
1	38 (43.2%)
2	50 (56.8%)

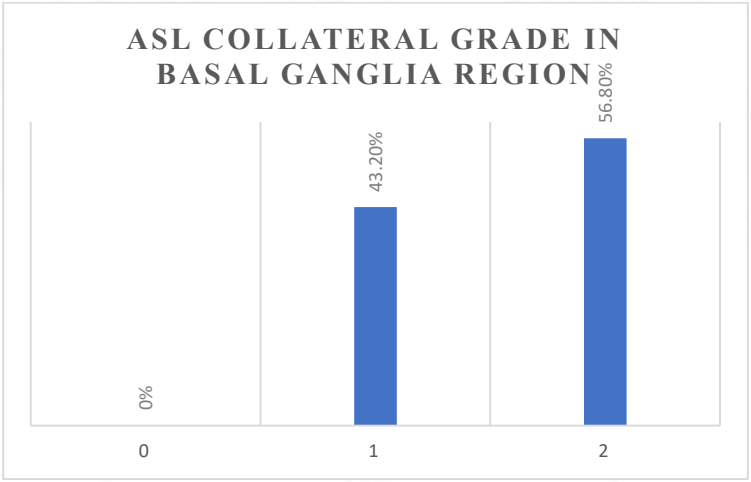

Figure 41: Frequency distribution of various grades of collaterals on ASL in basal ganglia region

Table 38: Frequency distribution of various grades of collaterals on ASL in M1 region

ASL collateral grade	N (%)
0	1 (1.1%)
1	42 (47.7%)
2	28 (31.8%)
3	17 (19.3%)

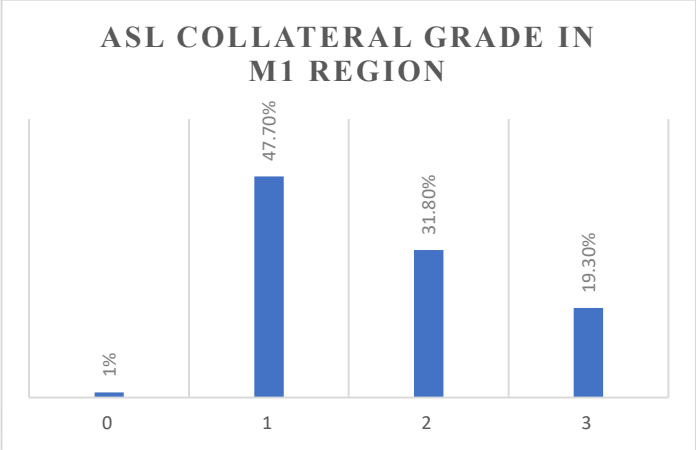

Figure 42: Frequency distribution of various grades of collaterals on ASL in M1 region

Table 39: Frequency distribution of various grades of collaterals on ASL in M2 region

ASL collateral grade	N (%)
0	4 (4.5 %)
1	57 (64.8%)
2	11 (12.5%)
3	16 (18.2%)

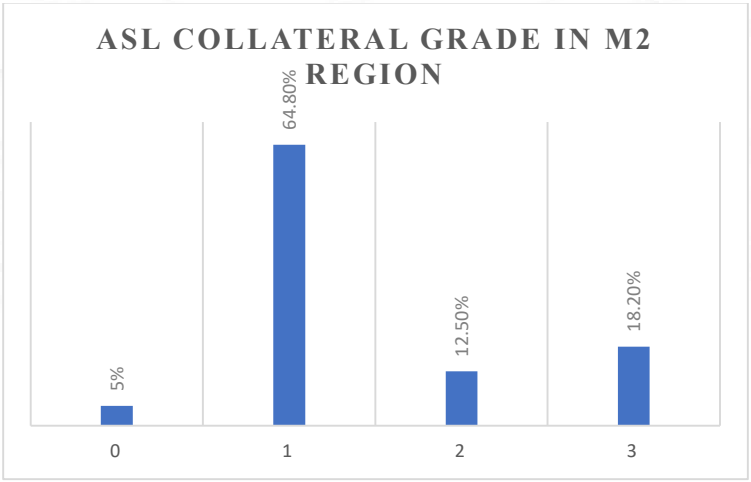

Figure 43: Frequency distribution of various grades of collaterals on ASL in M2 region

Table 40: Frequency distribution of various grades of collaterals on ASL in A1 region

ASL collateral grade	N (%)
0	0
1	43 (48.9%)
2	26 (29.5%)
3	19 (21.6%)

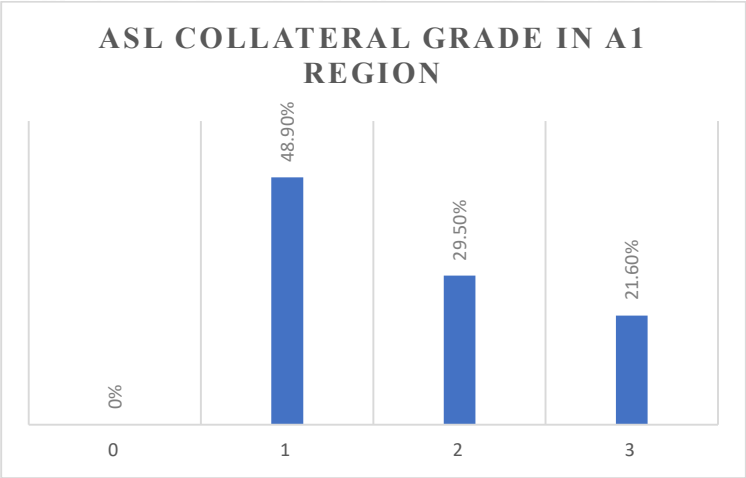

Figure 44: Frequency distribution of various grades of collaterals on ASL in A1 region

Table 41: Frequency distribution of various grades of collaterals on ASL in A2 region

ASL collateral grade	N (%)
0	0
1	40 (45.5%)
2	28 (31.8%)
3	20 (22.7%)

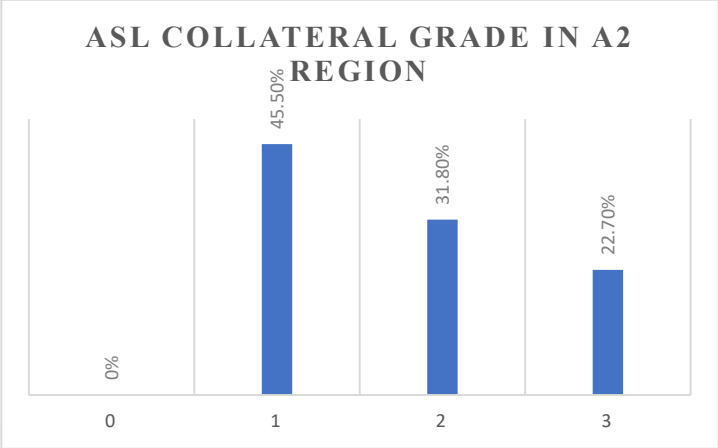

Figure 45: Frequency distribution of various grades of collaterals on ASL in A2 region

Table 42: Frequency distribution of various grades of collaterals on ASL in P1 region

ASL collateral grade	N (%)
0	0
1	11 (12.5%)
2	11 (12.5%)
3	66 (75%)

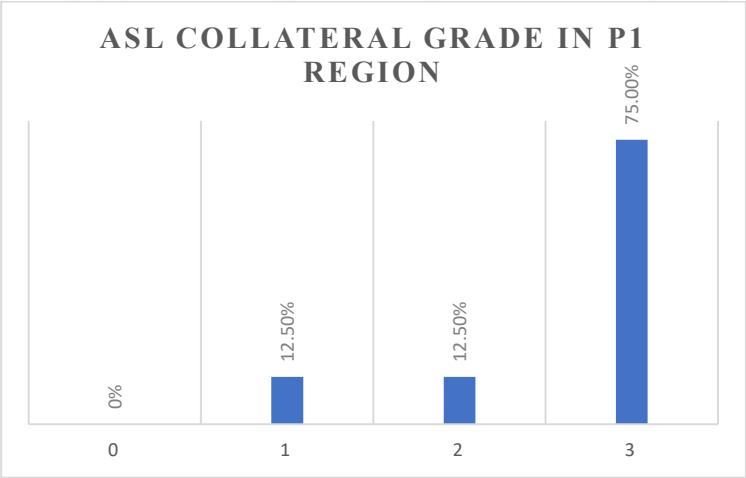

Figure 46: Frequency distribution of various grades of collaterals on ASL in P1 region

Table 43: Frequency distribution of various grades of collaterals on ASL in P2 region

ASL collateral grade	N (%)
0	1 (1.1%)
1	19 (21.6%)
2	2 (2.3%)
3	66 (75%)

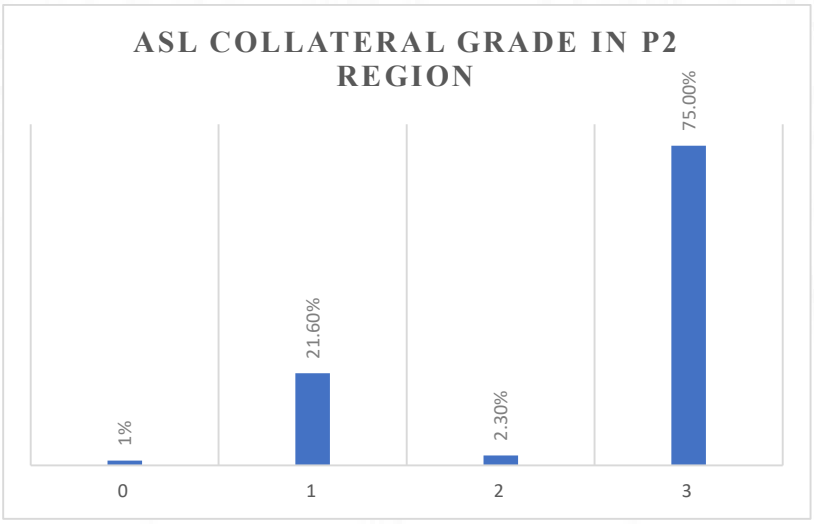

Figure 47: Frequency distribution of various grades of collaterals on ASL in P2 region

At various Suzuki grades, the degree of collaterals graded on ASL were compared at each ROI to look for change in collateral status on ASL with the DSA Suzuki stage. This is done to predict the collateral shift with increasing severity of the MMD. On chi-square test this change in collateral grading with Suzuki staging is statistically significant at all the ROIs ($p<0.001$).

Table 44: ASL collateral grading at Basal ganglia region across various Suzuki grades

	ASL Collateral grading at BG		
Suzuki grading	1	2	Total
0	0	7	7
1	2	8	10
2	4	9	13
3	8	16	24
4	22	7	29
5	2	3	5
Total	38	50	88

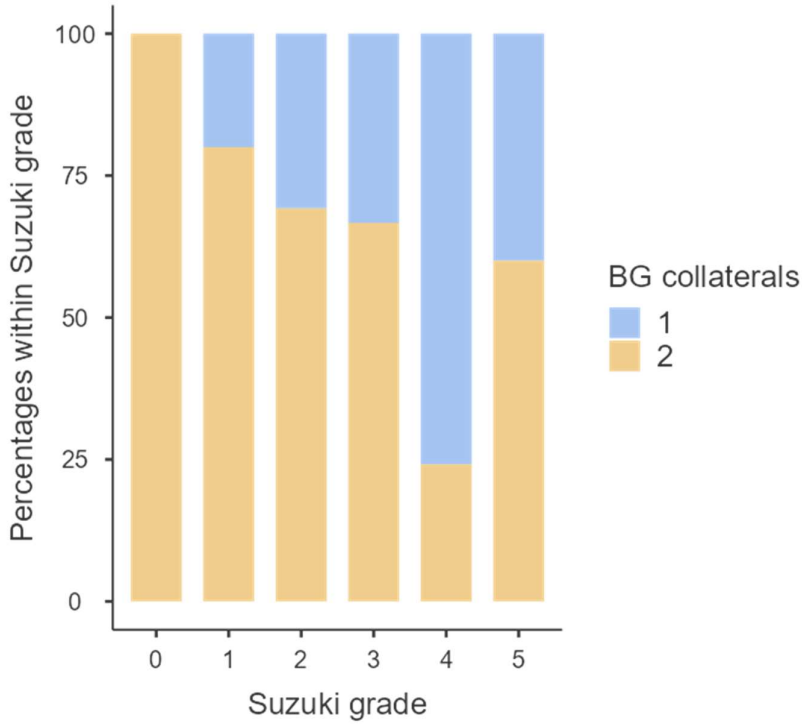

Figure 48: ASL collateral grading at Basal ganglia region across various Suzuki grades

Table 45: ASL collateral grading at M1 region across various Suzuki grades

	ASL Collateral grading at M1 region				
Suzuki grading	0	1	2	3	Total
0	0	0	0	7	7
1	0	1	2	7	10
2	0	3	7	3	13
3	0	13	11	0	24
4	1	22	6	0	29
5	0	3	2	0	5
Total	1	42	28	17	88

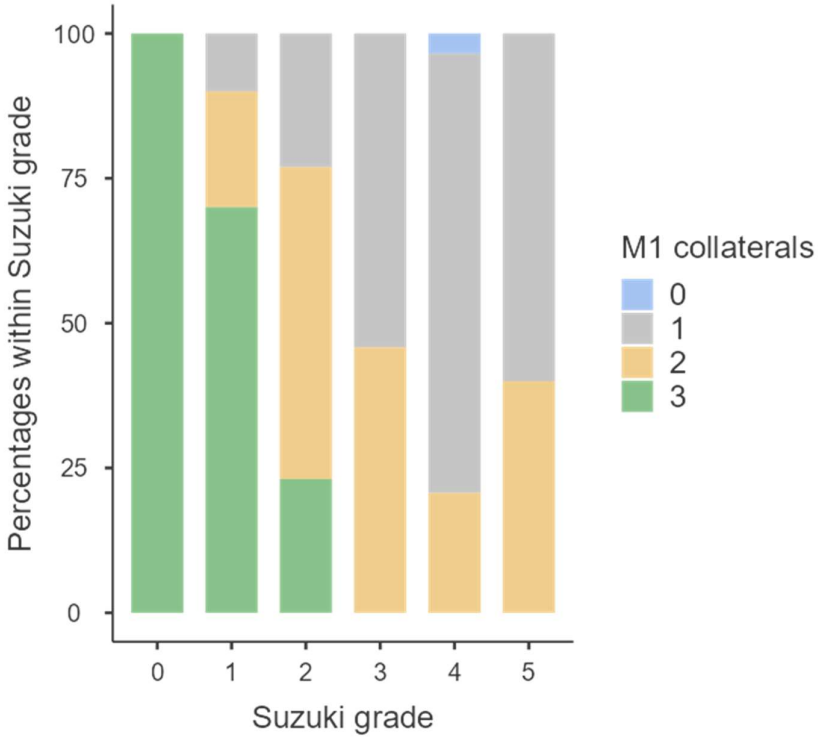

Figure 49: ASL collateral grading at M1 region across various Suzuki grades

Table 46: ASL collateral grading at M2 region across various Suzuki grades

	ASL Collateral grading at M2 region				
Suzuki grading	0	1	2	3	Total
0	0	0	0	7	7
1	0	1	2	7	10
2	0	9	2	2	13
3	1	18	5	0	24
4	3	26	0	0	29
5	0	3	2	0	5
Total	4	57	11	16	88

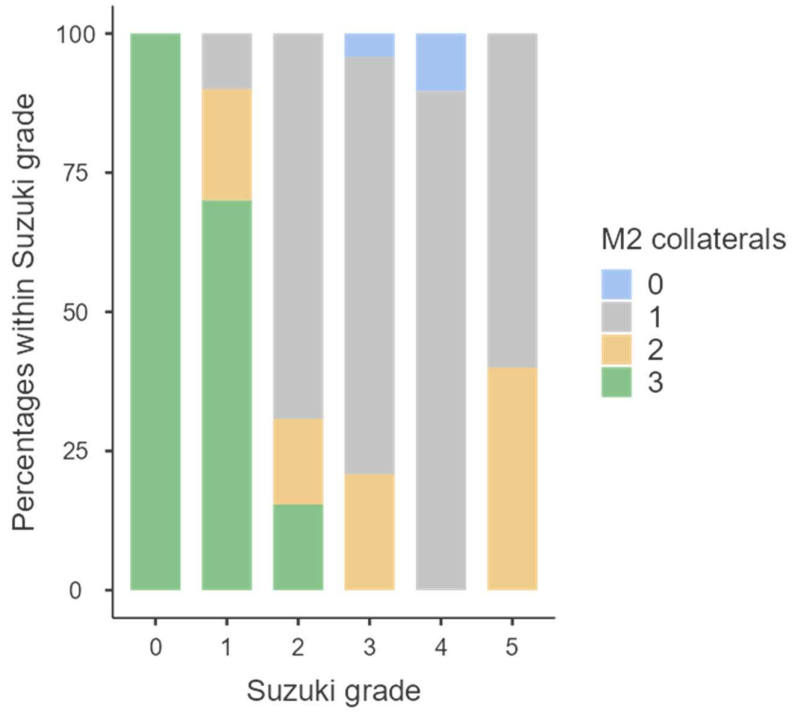

Figure 50: ASL collateral grading at M2 region across various Suzuki grades

Table 47: ASL collateral grading at A1 region across various Suzuki grades

	ASL Collateral grading at A1 region			
Suzuki grading	1	2	3	Total
0	0	0	7	7
1	3	2	5	10
2	3	8	2	13
3	12	9	3	24
4	22	5	2	29
5	3	2	0	5
Total	43	26	19	88

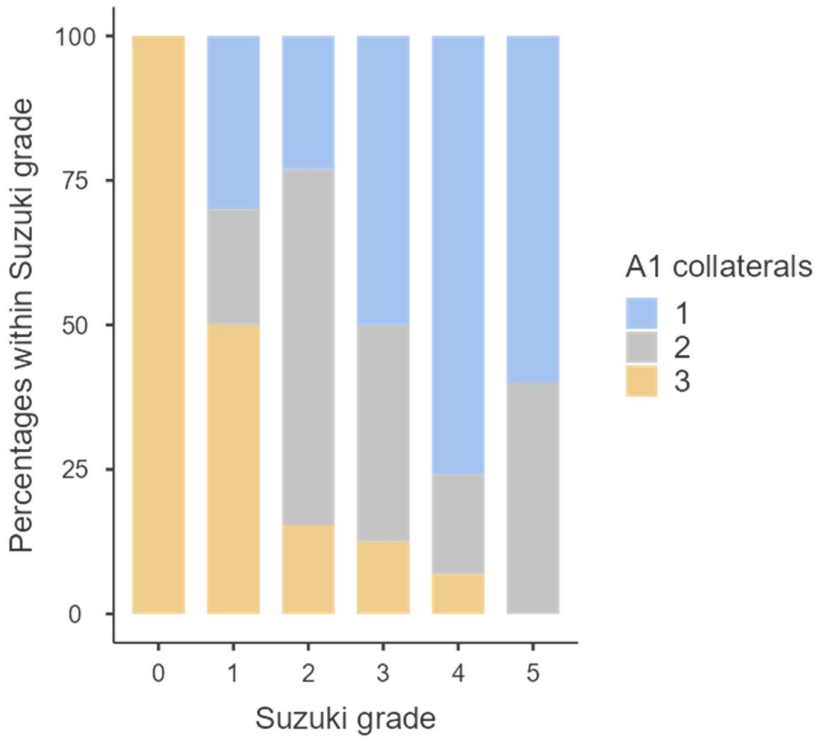

Figure 51: ASL collateral grading at A1 region across various Suzuki grades

Table 48: ASL collateral grading at A2 region across various Suzuki grades

	ASL collateral grading at A2 region			
Suzuki grading	1	2	3	Total
0	0	0	7	7
1	2	3	5	10
2	3	7	3	13
3	9	12	3	24
4	23	4	2	29
5	3	2	0	5
Total	44	28	20	88

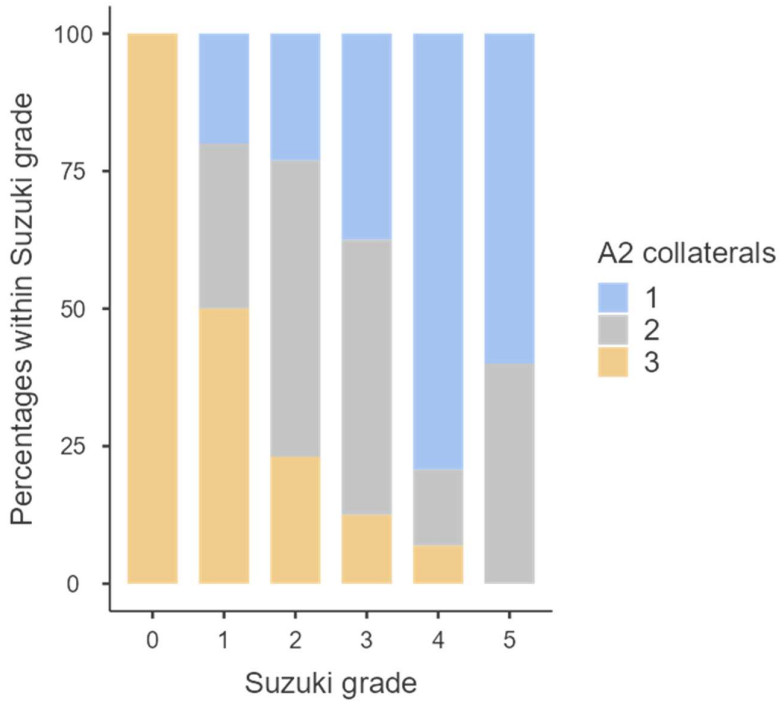

Figure 52: ASL collateral grading at A2 region across various Suzuki grades

Table 49: ASL collateral grading at P1 region across various Suzuki grades

	ASL collaterals in P1 region			
Suzuki grading	1	2	3	Total
0	0	0	7	7
1	0	1	9	10
2	0	0	13	13
3	0	3	21	24
4	11	6	12	29
5	0	1	4	5
Total	11	11	66	88

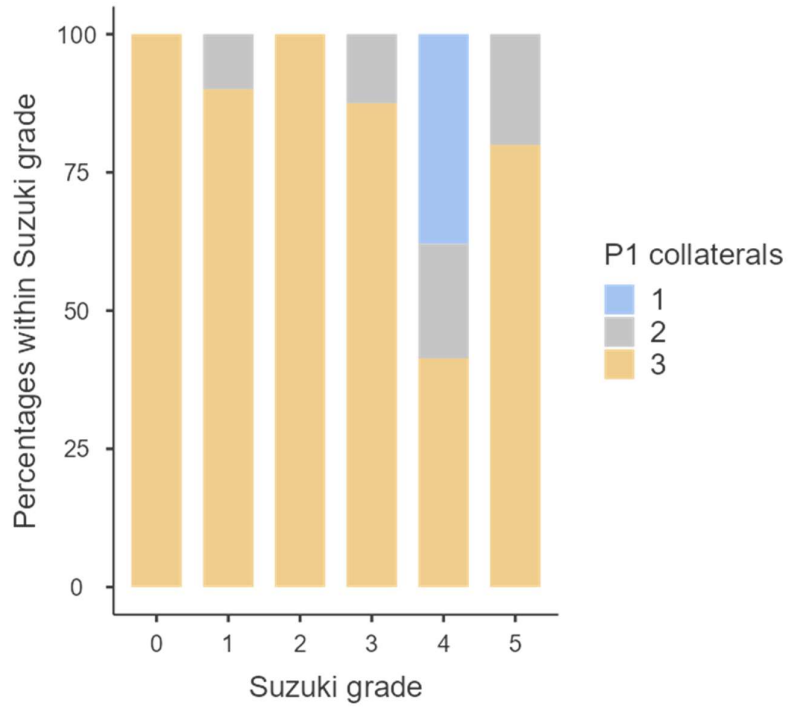

Figure 53: ASL collateral grading at P1 region across various Suzuki grades

Table 50: ASL collateral grading at P2 region across various Suzuki grades

	ASL collaterals at P2 region				
Suzuki grading	0	1	2	3	Total
0	0	0	0	7	7
1	0	0	1	9	10
2	0	0	0	13	13
3	0	3	0	21	24
4	1	16	0	12	29
5	0	0	1	4	5
Total	1	19	2	66	88

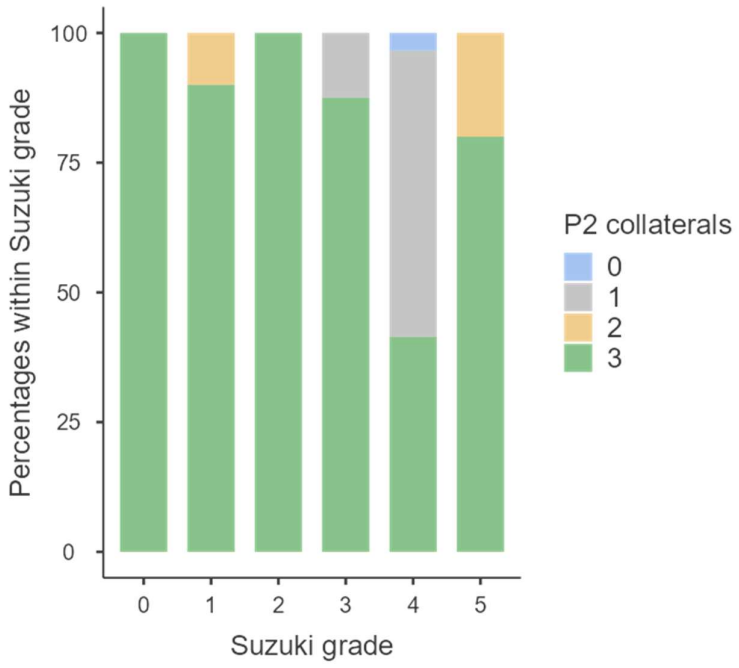

Figure 54: ASL collateral grading at P2 region across various Suzuki grades

Whether collateral grading using ASL can predict the collaterals graded using DSA was tested using Cohen Kappa's method, and it was found that ASL can be used to predict collaterals graded by DSA with very good agreement in all the ROIs ($p<0.001$). The kappa value was low when used for basal ganglia region, and this is may be due to use of 3 grades in ASL as opposed to 4 grades in DSA for basal ganglia region.

Table 51: Agreement between collateral grading using DSA and ASL

	Agreement %	Kappa	p-value
Basal ganglia	75%	0.577	<0.001
M1	93%	0.892	<0.001
M2	92%	0.855	<0.001
A1	94%	0.910	<0.001
A2	88%	0.806	<0.001
P1	98%	0.944	<0.001
P2	100%	1.000	<0.001

DISCUSSION

MMD is an uncommon cause of stroke in both pediatric and adult patients. The current study showed bimodal age distribution but no difference in gender predilection. Patients most commonly had ischemic presentation overall, while hemorrhagic presentation is more common in adults compared to the pediatric age group. While the most common presenting complaint is weakness of limbs, a significant proportion of patients also had seizures and headaches. Uncommon symptoms include syncope, behavioral changes, or ataxia. These findings are consistent with previous Indian studies. (Sadashiva et al., 2016; Sreenivasan et al., 2022; Sundaram et al., 2014) While the disease is unilateral in 7 patients, the remaining 39 patients had bilateral involvement. Among these, 17 patients had symptoms related to bilateral cerebral hemispheres at the time of evaluation, while the remaining had symptoms of a silent disease process in one hemisphere. Most of the patients had minor stroke as the manifestation or had low NIHSS and mRS at the time of evaluation. The mean interval between both the studies with either one obtained first is 21 days with a range of 1 day to 88 days.

Natural history of the progression of collaterals

The primary aim of the study was to determine the natural history of MMD with respect to collateral development and shifting. With the development of ischemia, the body tries to maintain perfusion through various mechanisms, including the development of collaterals, which may be in the form of the opening of preexisting vascular conduits or with the development of new collateral sprouts. (Maguida and Shuaib, 2023) This mainly occurs with long-standing ischemia, as in cerebrovascular intracranial atherosclerotic disease. A similar mechanism is also responsible for the characteristic collateral formation in MMD. In the initial stages of the disease, with the development of the progressive steno-occlusive disease

involving the distal ICA, hypoperfusion occurs in the areas surrounding the circle of Willis, eventually leading to a net-like collateral development in this region. (Suzuki, 1969) Collaterals in the basal brain region surrounding the circle of Willis are most prominent during Suzuki stage 3 of the MMD. (Yamamoto et al., 2019) However, with further disease progression (Suzuki stage IV and V), the leptomeningeal pial collaterals at the cortical surface and ECA collaterals are recruited. By this time (Suzuki stage V) usually, there is a reduction in the basal collaterals. With more advanced disease, as in Suzuki stage VI, all the Moyamoya collaterals disappear entirely, leaving a severe perfusion deficit. (Scott and Smith, 2009; Suzuki, 1969)

Much of this understanding has accrued from angiographic studies. There are no studies, except one (Yamamoto et al., 2019), which looked at the natural progression of the collateral shift with advancing disease. Yamamoto et al. described the shift of collaterals posteriorly with advancing disease. (Yamamoto et al., 2019) This study showed that in the early disease, most collateral circulation is derived from lenticulostriate branches and anterior choroidal artery. Then, the posterior basal vessels (posterior communicating artery and the posterior choroidal artery) dilate more with increased collaterals as the disease advances. This is because the posterior circulation is least involved in MMD, thus contributing most to the compensation to maintain the perfusion. However, this study only studied the basal and deep collaterals and did not study the perfusion and collateral status at the cortical level. Angiographic studies depict the structural changes occurring with the disease. But does this translate to the functional change that is expected with these structural changes is not well studied. Therefore, we have employed the MR-ASL technique to study the change in perfusion status with changing disease stages. To the best of our knowledge, the current study is the first to look into the association of the progression of the disease with the collateral development and shift both at basal and cortical levels across all the Suzuki stages in MMD both structurally (by DSA) as well as functionally (by ASL). The maximum time interval between these two

investigations was arbitrarily decided as three months, assuming periods longer than that may lead to disease progression, thereby affecting the imaging findings.

The study included patients with normal cerebral hemispheres (n=7) and those with all subsequent stages of the disease but lacked any patients with Suzuki stage VI. The sample size of 81 diseased cerebral hemispheres, spanning Suzuki grades 1 through 5, gives a fair sample size to study the disease progression with respect to collaterals across all the stages. In the current study, the collaterals started appearing from Suzuki grades 1 and 2 and were maximum in stage 3. Following this, they decreased in all the regions studied. This change was statistically significant on the Chi-square test ($p<0.001$). The collaterals were maximum in the basal region, as depicted by a greater number of patients having grade 2 collaterals compared to grade 1 collaterals in Suzuki grade 3 and 4 in BG, M1, and A1 regions. This is in contrast to the surface collaterals observed in M2 and A2 regions, where a greater number of patients had grade 1 collaterals compared to grade 2 collaterals in Suzuki grades 3 and 4.

These findings are in agreement with the previous understanding that the hypoperfusion is maximum at the cortical surface as the disease progresses. (Scott and Smith, 2009) Togao et al. used MR perfusion imaging and showed that the mean transit time (MTT) corresponded to the degree of the stenosis of the ICA and PCA in the basal ganglia and ROIs in medial and posterior frontal cortical surfaces, where the cortical ROIs were also placed at the basal ganglia level.(Togao et al., 2006) In the current study, in addition to cortical ROIs at the basal ganglia level (M1, A1, and P1), ROIs were also placed in the supra-ganglionic level (M2 and A2), which showed the least collaterals with the disease progression. The current study has shown that posterior circulation involvement in MMD is uncommon and, in the advanced disease state, contributes to the collateral blood supply in some. These findings are similar to Yamamoto et al.'s previous study, which demonstrated an anterior-to-posterior shift

of basal collaterals with advancing disease.(Yamamoto et al., 2019)

The current study has depicted the development and disappearance of collaterals in various ROIs using both the DSA collateral grading and the ASL collateral grading. This proves that the structural changes occurring with progressing disease are accompanied by corresponding functional perfusion change, as the ASL shows. The current study did not employ the quantification of CBF on ASL. Accurate quantification of CBF could be obtained with multi-delay ASL, which was not available in our retrospectively studied patients. So, we have employed qualitative collateral grading on ASL images as a surrogate for the perfusion assessment as used in previous studies.(Wang et al., 2014; Zaharchuk et al., 2011) For quantitative measures, we have used the ASL signal intensity ratio, which uses the signal value obtained from the ROI in these regions as the numerator and the signal value from the ipsilateral cerebellum as the denominator. Only 78 hemispheres scans had the source images available in the hospital records. Hence, only 78 of the 88 hemispheres were used to calculate ASL-SIR. The Suzuki stage has also had a statistically significant correlation with the ASL-SIR in all the ROIs (except BG and P1). At basal ganglia, the surrounding white matter may have confounded the ASL-SIR measurement. The mean ASL-SIR was found to be effective in differentiating collateral grades 0 from 1, 0 from 2, and 1 from 2, while it is ineffective in differentiating collateral grades 2 from 3. Thus, when perfusion if dichotomized as low to moderate vs. good, ASL-SIR can be used to differentiate these groups, though the differentiation of whether the good perfusion is because of normal circulation or secondary to collateral development cannot be done.

Role of ASL in determining the collaterals

Previous studies where ASL was employed to assess perfusion in MMD showed that the cerebral blood flow (CBF) calculated by ASL had a good correlation with the CBF calculated

by CT perfusion (CTP) or Xe-CT perfusion or dynamic susceptibility contrast MRI (DSC-MRI).(Fan et al., 2017; Togao et al., 2023; Wang et al., 2014; Zaharchuk et al., 2011). Thus, ASL can be used as an alternative for predicting the CBF without employing any contrast agent like with CTP or PET or Xe-CT scans in MMD. Two of these studies have also used visual subjective ratings to determine perfusion and have proven to be effective. Zaharchuk et al. have formulated a new grading system for grading collaterals by visual impression using both DSA and ASL. The same study has also compared the CBF from ASL and Xe-CT scans and found they are correlating. The study also showed that the ASL collateral score increased as the CBF increased. (Zaharchuk et al., 2011) The current study has also used a similar collateral grading system. Wang et al., in their study, used pseudo-continuous ASL and compared it with CTP in determining the accuracy of predicting the perfusion. They have also used a subjective scale from 0 to 3 for determining the severity of hypoperfusion within predefined regions for both ASL and CTP, and found they a statistically significant correlation between the methods and also with the quantitative measurements of the perfusion. (Wang et al., 2014) Therefore, the ASL technique can be employed to make a qualitative assessment of the perfusion, which in turn correlates with qualitative perfusion measures, as shown in these two studies.

The current study has shown good agreement between qualitative collateral grading using DSA and ASL in all the studied regions. This is in line with the results of the Zaharchuk et al. study, where a moderate to strong agreement was obtained in the consensus reading of the qualitative collateral grading done by two separate neuroradiologists. The study also showed a 0.83 sensitivity and 0.82 specificity in identifying collaterals with ASL as compared to DSA. (Zaharchuk et al., 2011) The agreement between the methods is higher in the current study compared to Zaharchuk et al. One principal difference is that in the Zaharchuk et al study, only cortical ROIs were taken in the regions used for ASPECTS scoring. They avoided subcortical and white matter regions as the visualization of blush on DSA and ASL signal on

imaging may be difficult. However, in the current study, we chose to select ROIs in the basal ganglia level as well, as this area is the first and foremost, as well as maximum collateral development.

With the above results, it can be said that ASL can be used as effective alternative to determine the collaterals and perfusion in the various regions of the brain, and the results are comparable to gold standard DSA or other perfusion techniques like CTP, PET, etc. Though DSA is the gold standard for MMD diagnosis, it is an invasive procedure requiring contrast infusion and has difficulty in obtaining images in pediatric patients, sometimes requiring anesthesia. These can themselves precipitate stroke in MMD patients and hence may be avoided. ASL technique has the advantages of being able to obtain without the need for skilled interventional radiologists, without exposure to contrast, and also the advantage of using serially to follow-up the patients to study the disease progression and also to determine the timing of revascularization. Also, the perfusion deficit is maximum around the circle of Willis in the initial stages of the disease, which is corrected with the development of the collaterals. As the disease advances, the basal collaterals disappear, and the cortical regions have the highest hypoperfusion.

Strengths:

1. This is the first study to look into the natural history of the MMD with respect to collaterals, both basal as well as superficial cortical, across various Suzuki stages.
2. This is the first study to employ the MR-ASL technique in addition to DSA for determining the functional change i.e., change in perfusion status with the disease progression, in addition to the structural change, i.e., collaterals development and disappearance.

3. It is an easily reproducible collateral grading system used for both DSA and ASL techniques.
4. Two independent investigators have rated the DSA and ASL collaterals, and consensus values are used for the comparison.

Limitations

1. A small sample size precludes non-uniform representation of different Suzuki stages
2. Longitudinal follow-up of individual patients was not done
3. Single centre study

In the future, large multi-center pooled cohorts may be used to increase the sample size and more uniform representation of all age groups, ethnicities, and all MMD stages. Longitudinal follow-up studies with ASL may be done, which, if proved effective, can be used as a non-invasive, simple, and easily reproducible test for determining the collateral status and the disease progression, thereby helping in determining the treatment plan and timing of revascularisation.

CONCLUSION

MMD is a progressive steno-occlusive disease of the ICAs with varied clinical presentation. The perfusion deficit in MMD is dynamic. MMD collaterals typically appear in the basal region in stage 3 disease, and with further progression, collaterals disappear with maximum hypoperfusion in the cortical areas in the advanced stages. MR-ASL may be used as a simple, safe, effective, and reproducible alternative for DSA in determining the collaterals and perfusion status in MMD patients without untoward effects like contrast or radiation exposure.

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ANNEXURE -I

Curriculum Vitae – Dr S M Krishna Mohan M

Name: Dr. Sambha Murthy Krishna Mohan Mavuru

D.O.B.: 11/04/1990

Sex: Male

Educational Qualifications: MBBS, MD (General Medicine)

Current Designation: Senior Resident (Third year), Department of Neurology

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Current and previous positions (most recent position first)		
Month and Year	Title	Institution/Company, Country
01.01.2021 – today	Senior resident in the Department of Neurology, SCTIMST	Sree Chitra Tirunal Institute of Medical Sciences and Technology
23.07.2020 to 15.12.2020	Consultant Physician	Indus Hospital, Visakhapatnam, Andhra Pradesh, India
12-06-2019 to 11-06-2020	Senior Resident in the department of General Medicine	Andhra Medical College, Visakhapatnam, India
2016-2019	Junior Resident, Department of General Medicine	Rangaraya Medical College, Kakinada, Andhra Pradesh, India
Brief summary of relevant research experience: Research done as a Neurology resident:		

Finished projects as Principal Investigator / First author:

1. Perfusion Patterns in Varying Angiographic stages (Suzuki Grading) of Indian Moyamoya patients. [submitted as thesis for DM neurology degree]

2. Post COVID-19 Neurological Spectrum– Experience from a single centre. Presented at NSI-CON 2022 (Kerala Chapter), submitted for publication (under peer review)

3. 'Precuneus epilepsy – a distinct presurgical entity? Electroclinical profile and outcomes in precuneal epilepsy – a retrospective cohort' – presented at ECON 2023 (National epilepsy conference of India), being prepared for publication. [Largest series in the world on Precuneus epilepsy and 2nd largest precuneus epilepsy surgical cohort]

4. 'CNVs in refractory epilepsy – a diagnostic odyssey' – accepted for poster presentation at ILAE Congress 2023, Dublin, Ireland; being prepared for publication [first and the largest study on CNVs in Indian refractory epilepsy patients]

Finished projects as Co-investigator / one of the authors:

1. Sequential Multimodality Stimulation – A Novel intervention strategy for post stroke Hemineglect: Results from a randomised controlled trial – 2nd author; submitted for publication (under peer review)

2. Primary focal dystonias and response to botulinum toxin' – 3rd author, being prepared for publication

3. Primary CNS Angitis – a retrospective cohort study from South India. – being prepared for publication. [4th largest PACNS cohort in the world]

Current project/s at hand as Principal Investigator:

Clinical Profile of Immunotherapy Responsive Chronic Progressive Axonal Polyneuropathy

Research done as a medical (MBBS) student or during MD (general medicine) residency:

1. MD thesis project on 'Prognostic value of HbA1c in nondiabetic acute STEMI in comparison to clinical TIMI score.'
2. Poster Presentation at AP-APICON 2018: A Case Of Atypical Paraneoplastic Syndrome Associated With Anti-Yo Antibodies. [Received BEST POSTER AWARD].
3. Paper Presentation at APICON 2019: Thrombolysis In Acute Ischemic Stroke With Tenecteplase In A Government Tertiary Hospital In Andhra Pradesh.
4. Paper presentation at IPHA state and national conference 2012: Hospital Antibiogram of Government General Hospital, Kakinada

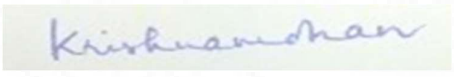
Publications:

Reversible Cerebral Vasoconstriction Syndrome with Spontaneous Spinal Subdural Hemorrhage—a Perplexing Conundrum!!!. https://doi.org/10.1177/25166085231172869

Book chapter in CME book for NSI conference 2023 – 'Alteplase vs. Tenecteplase for Acute Ischemic stroke management'

Many other case reports and the above mentioned studies are either submitted or being prepared for publication.

Trivandrum

Signature: 

27.08.2023

Curriculum vitae (CV)- Dr. Viswanadh K S V G

Last Name -K S V G	**First Name** - VISWANADH	
Date of Birth (dd/mm/yy)- 24/04/1990		**Sex**- MALE
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Phone number-8106645664		**Alternative Number**- 9496937773
		Email- viswanath2481990@gmail.com

Academic Qualifications (Most recent qualification first)

Degree/Certificate	Year	Institution, Country
MD RADIO DIAGNOSIS	2016-2019	GUNTUR MEDICAL COLLEGE, GUNTUR, ANDHRA PRADESH
MBBS	2008-2014	SRI VENKATESWARA MEDICAL COLLEGE, TIRUPATI, ANDHRA PRADESH

Current and previous positions (most recent position first)		
Month and Year	Title	Institution/Company, Country
JAN 2021 to current	SENIOR RESIDENT	SCTIMST, THIRUVANANTHAPURAM, INDIA
2019 to 2020	SENIOR RESIDENT	KAMINENI ACADEMY OF MEDICAL SCIENCES AND RESEARCH CENTRE, HYDERABAD.

Brief summary of relevant research experience:

Presented a poster titled Evaluation of arteriovenous malformations of the brain with CT Angiography: A case report at AOCR 2018

1. MRI evaluation of traumatic ACL and associated injuries of knee with arthroscopy correlation; Balaji Varaprasad Mallula, Annapurna S, Srinadh Boppana, Ravi Raja Sankuri, Viswanadh KSVG and Jaya Prasad PS; International Journal of Radiology and Diagnostic Imaging

Signature: Viswanadh KSVG

Date: 05-01-2023

Place: THIRUVANANTHAPURAM

Curriculum Vitae – Dr Bejoy Thomas

Last Name **Thomas**	First Name **Bejoy**	Middle Name
Date of Birth (dd/mm/yy) **23.05.1969**		Sex **Male**
Study Site Affiliation (e.g. Principal Investigator, Co-Investigator, Coordinator) PI, Co PI		
Professional Mailing Address (Include Institution name)		Study Site Address (Include Institution name)
Professor, Department of Imaging Sciences and Interventional Radiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala, India, 695011.		**Department of Imaging Sciences and Interventional Radiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala, India, 695011.**
Telephone (Office): **+ 91 471 2524117**		Mobile Number:**+ 91 9447719481**
Telephone (Residence):**+ 91 471 2440687**		Email bejoy@sctimst.ac.in
Academic Qualifications (Most recent qualification first)		
Degree/Certificate	Year	Institution, Country
Clinical Fellowship, Pediatric Neuroradiology	2009	The Hospital for Sick Children, University of Toronto, ON, **Canada**
BOYSCAST' Fellowship	2004	University Hospital, Gasthuisberg, Katholieke Universiteit Leuven, **Belgium.**
PDCC (Neuro and Vascular Radiology)	1998	Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, **India**
DNB (Radiodiagnosis)	1997	National Board of Examinations, **India**
MD (Radiodiagnosis)	1997	N.H.L. Municipal Medical College, Gujarat University, **India**
MBBS	1993	Government Medical College Kottayam, Mahatma Gandhi University, Kottayam, Kerala, **India**.
Details of professional registration : (MCI/State Registration/Bar Council/DCI/etc including Registration Number and Year of Registration **TCM Reg No: 20483 year 1993**		

Curriculum vitae – Dr Sajith

Last Name: Sukumaran	First Name: Sajith	Middle Name
Date of Birth: 22/05/1973		Sex: Male
Study Site Affiliation: Co-Principal Investigator		
Professional Mailing Address (Include Institution name)		Study Site Address (Include Institution name)
Professor Dept. of Neurology, SCTIMST		Dept. of Neurology, SCTIMST
Telephone (Office): 04712524184		Mobile Number: 9947488294
Telephone (Residence): 04712597696		Email: sajith@sctimst.ac.in
Academic Qualifications (Most recent qualification first): Stroke Fellowship (UCLH), Fellowship in Interventional Neurology and Stroke, DM Neurology, DipNB (Gen. Medicine), MD (Gen. Medicine), MBBS		
Degree/Certificate	**Year**	**Institution, Country**
Stroke Fellowship	2013	UCLH, London, UK
Fellowship in Interventional Neurology and Stroke	2006	SGRH, New Delhi, India
DM Neurology	2015	SCTIMST, India
DipNB (Internal Medicine)	2002	National Board, New Delhi
MD (General Medicine)	2001	Govt. Med. College, Tvm, India
MBBS	1995	Govt. Med. College, Tvm, India
Details of professional registration : (MCI Registration): Reg.No: 24716 (Travancore Cochin Medical Council, 1996)		
Current and previous positions (most recent position first)		
Month and Year	Title	Institution/Company, Country
2017 to date	Professor, Neurology	SCTIMST
2013-2017	Addl. Professor, Neurology	SCTIMST
2011-2013	Asso. Professor, Neurology	SCTIMST
2007-2011	Asst. Professor, Neurology	SCTIMST
2006-2007	Adhoc Consultant, Neurology	SCTIMST
Brief summary of relevant research experience: 18 journal publications. Two completed extramural funded projects as Co-PI, one ongoing extramurally funded project as PI, one intramurally funded completed BMT project as PI, more than 20 other IEC approved completed projects and 2 ongoing IEC approved projects as PI/Co-PI.		
Current project/s at hand: One extramural funded projects, 2 non funded IEC approved projects		
Signature: 		Date: 10-07-2021 Place: Thiruvananthapuram

APPENDIX – A: IEC APPROVAL FORM

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)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-21)

SCT/IEC/1847/FEBRUARY/ 2022 25.04.2022

Dr. SM Krishna Mohan M
Senior Resident
Department of Neurology
SCTIMST, Thiruvananthapuram

Dear Dr. Krishna Mohan,

The Institutional Ethics Committee held on 19th February, 2022, reviewed and discussed your application to conduct the study titled "**PERFUSION PATTERNS IN VARYING ANGIOGRAPHIC STAGES (SUZUKI GRADING) OF INDIAN MOYAMOYA PATIENTS**" (IEC/1847).

The following members of the Ethics Committee were present at the meeting held on 19th February, 2022

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Prof. C.C. Kartha	MBBS,MD	Male	Basic Medical Scientist (Chairman)	No
2.	Dr. Kala Kesavan P	MBBS,MD	Female	Basic Medical Scientist	No
3.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
4.	Dr. Pradeep S	MBBS, MD	Male	Basic Medical Scientist	No
5.	Dr. P. Manickam	BSMS, MSc (Epid).,PhD	Male	Health Science Expert/ Social Scientist	No
6.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
7.	Adv. N Anand	BAL, L.LB	Male	Legal Expert	No
8.	Adv. Priya Kaimal	LLM, MBL	Female	Legal Expert	No
9.	Dr. Harikrishna Varma PR	Ph.D (Materials Science)	Male	Medical Technology	Yes
10.	Dr. Narayanan Namboodiri. K K	MBBS,MD,DM	Male	Clinician	Yes
11.	Dr. Ashalatha R	MBBS, MD,DM	Female	Clinician	Yes
12.	Dr. Biju Soman	MBBS,MD, DPH, MSc, DLSHTM	Male	Basic Medical Scientist	Yes
13.	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes

The following documents were reviewed:

Original submission

1. *Checklist Form*
2. *Covering letter addressed to the Chairperson, IEC, SCTIMST*
3. *Covering letter addressed to the Chairperson, IEC, SCTIMST forwarded by HOD*
4. *IEC Application form*
5. *Project Proposal*
6. *Declaration form*
7. *Abbreviations*
8. *Informed Consent Form*
9. *Patient Information Sheet in English and Malayalam*
10. *Parental Consent and Assent Form Malayalam*
11. *CV of PI and Co-PIs*
12. *Proforma*
13. *SRC Recommendation Letter*

Revised submission

1. *Covering letter addressed to the Member Secretary, IEC, SCTIMST*
2. *Checklist Form*
3. *Covering letter addressed to the Chairperson, IEC, SCTIMST*
4. *Covering letter addressed to the Chairperson, IEC, SCTIMST forwarded by HOD*
5. *IEC Application form*
6. *Project Proposal*
7. *Declaration form*
8. *Abbreviations*
9. *Informed Consent Form*
10. *Patient Information Sheet in English and Malayalam*
11. *Parental Consent and Assent Form Malayalam*
12. *CV of PI and Co-PIs*
13. *Proforma*

IEC Decision

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

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

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– DATA COLLECTION PROFORMA

Serial No.

Age

Gender

Presenting complaints – weakness / seizure / headache / sensory symptoms / vertigo/ etc

History of TIA - Yes / No

Admission NIHSS

Admission mRS

Symptomatic side – right / left / both / neither

Interval between DSA and MR-ASL

Type of stroke – Ischemic / Hemorrhagic / neither

DSA findings:

	Right	Left
Suzuki stage		
Collateral grading		
BG		
M1		
M2		
A1		
A2		
P1		
P2		

ASL findings

	Right			Left		
	Signal intensity	SIR	Collateral grade	Signal intensity	SIR	Collateral grade
Cerebellum						
BG						
M1						
M2						
A1						
A2						
P1						
P2						

APPENDIX C - DATA MASTER CHART

S.No.	Age	Gender	Weaknes	Seizure	Headacl	Paresthe	Vertigo	Behavio	Ataxia	Adm NIH	Adm mF	sympton	I/H	Infarct/bl	TIA	interval c	Suzu	DSA BG	DSA M1	DSA M2	DSA A1	DSA A2	DSA P1	DSA P2	ASL Cer	ASL BG	ASLR BI	ASL M1	ASLR M	ASL M2	ASLR M	ASL A1	ASLR A	ASL A2	ASLR A	ASL P1	ASLR P	ASL P2	ASLR P	AC BG	AC M1	AC M2	AC A1	AC A2	AC P1	AC P2
1	27	1	1	0	0	0	0	0	0	3	2	2	2	1	0	18	5	1	1	2	1	2	1	2	576	566	0.98	594	1.03	634	1.1	517	0.89	660	1.14	884	1.53	673	1.16	2	2	1	1	1	2	2
2	27	1	1	0	0	0	0	0	0	3	2	2	2	1	0	18	1	1	2	2	2	2	3	3	459	471	1.02	543	1.18	678	1.47	497	1.08	552	1.2	796	1.73	740	1.61	2	2	2	2	2	3	3
3	8	1	0	0	1	0	0	0	0	0	0	3	1	1	0	5	3	2	2	2	1	2	3	3	569	736	1.29	939	1.47	592	1.02	252	0.44	498	0.87	611	1.07	660	1.15	2	2	2	1	2	3	3
4	8	1	0	0	1	0	0	0	0	0	0	3	1	1	0	5	3	1	1	1	1	1	3	3	498	593	1.19	603	1.21	540	1.08	285	0.57	477	0.95	668	1.34	721	1.44	1	1	1	1	2	3	3
5	10	2	1	0	0	0	0	0	0	0	0	3	1	0	1	80	5	2	2	2	2	2	3	3	722	852	1.18	701	0.97	852	1.18	718	0.99	765	1.05	882	1.22	872	1.2	2	2	2	2	2	3	3
6	10	2	1	0	0	0	0	0	0	0	0	3	1	0	1	80	5	1	1	2	2	2	3	3	688	767	1.12	591	0.85	813	1.18	780	1.13	774	1.13	879	1.27	720	1.04	2	1	2	2	2	3	3
7	27	2	0	0	0	0	1	0	0	0	0	3	1	1	1	44	5	1	1	1	1	1	3	3	680	739	1.08	467	0.68	394	0.57	443	0.65	437	0.64	621	0.91	781	1.14	1	1	1	1	1	3	3
8	27	2	0	0	0	0	1	0	0	0	0	3	1	1	1	44	5	1	1	1	1	1	3	3	661	603	0.91	559	0.84	305	0.46	417	0.63	409	0.62	635	0.96	815	1.23	1	1	1	1	1	3	3
9	13	2	0	1	0	0	0	0	0	0	0	3	1	1	0	1	4	1	1	1	1	1	2	1	704	522	0.74	550	0.78	435	0.61	564	0.8	472	0.67	683	0.97	564	0.8	1	1	1	1	1	2	1
10	13	2	0	1	0	0	0	0	0	0	0	3	1	1	0	1	4	1	1	1	1	1	1	1	631	491	0.77	582	0.92	212	0.33	416	0.66	314	0.49	749	1.18	447	0.71	1	1	1	1	1	2	1
11	45	2	0	0	1	0	0	0	0	0	0	1	2	1	0	15	3	2	2	2	2	2	3	3	626	472	0.75	507	0.81	376	0.6	601	0.96	661	1.05	609	0.97	630	1	2	2	1	2	2	3	3
12	45	2	0	0	1	0	0	0	0	0	0	1	2	1	0	15	0	3	3	3	3	3	3	3	580	567	0.97	581	1	584	1.01	594	1.03	656	1.13	655	1.13	719	1.24	2	3	3	3	3	3	3
13	10	2	1	0	0	0	0	0	0	4	3	3	1	1	0	62	3	1	1	0	1	2	2	1	632	428	0.68	227	0.36	117	0.18	226	0.36	641	1.01	777	1.23	472	0.75	1	1	0	1	2	2	1
14	10	2	1	0	0	0	0	0	0	4	3	3	1	1	0	62	3	1	1	1	2	1	2	1	680	460	0.67	335	0.49	305	0.45	432	0.64	244	0.36	760	1.12	357	0.53	1	1	1	1	1	2	1
15	8	1	0	1	0	0	0	0	0	0	0	3	1	1	0	48	3	2	2	2	2	2	3	3	673	880	1.31	578	0.86	471	0.7	614	0.91	609	0.9	637	0.94	840	1.25	2	1	1	2	2	3	3
16	8	1	0	1	0	0	0	0	0	0	0	3	1	1	0	48	4	2	2	1	1	1	3	3	645	893	1.38	629	0.97	393	0.61	498	0.77	495	0.73	756	1.17	687	1.06	2	2	1	1	1	3	3
17	31	1	0	1	0	0	0	0	0	1	2	2	2	1	0	60	3	2	2	2	2	2	3	3	593	562	0.95	579	0.97	550	0.93	536	0.9	567	0.96	705	1.18	731	1.23	2	2	2	2	2	3	3
18	31	1	0	1	0	0	0	0	0	1	2	2	2	1	0	60	2	1	2	1	2	3	3	3	493	479	0.97	429	0.87	416	0.84	413	0.84	445	0.9	522	1.06	603	1.22	1	1	1	2	2	3	3
19	8	2	1	1	0	0	0	1	0	2	1	3	1	1	0	46	4	1	1	1	1	1	3	3	504	483	0.96	420	0.83	438	0.87	306	0.6	422	0.84	532	1.05	567	1.13	1	1	1	1	1	3	3
20	8	2	1	1	0	0	0	1	0	2	1	3	1	1	0	46	2	3	3	3	2	3	3	3	458	553	1.21	562	1.23	542	1.18	423	0.92	598	1.3	553	1.21	550	1.2	2	3	3	1	3	3	3
21	33	1	1	0	0	0	1	0	0	0	0	2	1	1	1	4	3	2	2	2	2	2	3	3	450	431	0.96	451	1	588	1.24	415	0.92	508	1.13	435	0.97	567	1.26	2	2	2	2	2	3	3
22	33	1	1	0	0	0	1	0	0	0	0	2	1	1	1	4	3	2	2	2	3	3	3	3	445	422	0.94	448	1.01	482	1.08	470	1.05	583	1.31	500	1.12	551	1.24	2	2	2	3	3	3	3
23	50	1	1	0	0	0	0	0	0	0	0	1	1	1	1	4	4	1	1	1	1	1	1	1	548	405	0.74	446	0.81	328	0.59	231	0.42	447	0.82	295	0.54	300	0.55	1	1	1	1	1	1	1
24	50	1	1	0	0	0	0	0	0	0	0	1	1	1	1	4	1	3	3	3	3	3	3	3	547	474	0.87	535	0.98	559	1.02	562	1.03	534	0.97	718	1.31	664	1.21	2	3	3	3	3	3	3
25	40	2	0	1	0	1	0	0	0	0	0	1	1	1	1	1	4	1	1	1	1	1	3	3	511	373	0.73	352	0.68	245	0.48	278	0.54	295	0.58	679	1.33	594	1.16	1	1	1	1	1	3	3
26	40	2	0	1	0	1	0	0	0	0	0	1	1	1	1	1	4	1	1	1	1	1	3	3	454	340	0.75	325	0.72	225	0.49	368	0.81	296	0.65	568	1.25	534	1.18	1	1	1	1	1	3	3
27	8	1	0	0	1	0	0	0	0	0	1	0	0	0	0	3	2	2	2	1	2	2	3	3	753	990	1.31	1095	1.45	602	0.8	841	1.12	868	1.18	936	1.24	806	1.07	2	2	1	2	2	3	3
28	8	1	0	0	1	0	0	0	0	0	1	0	0	0	0	3	4	1	1	1	2	2	3	3	614	647	1.05	450	0.73	386	0.63	834	1.35	1001	1.63	789	1.28	729	1.18	1	1	1	2	2	3	3
29	7	2	0	0	0	1	0	0	0	1	1	2	1	0	1	1	1	3	3	3	3	3	3	3	624	721	1.15	775	1.24	788	1.26	681	1.09	691	1.11	765	1.22	888	1.42	2	3	3	3	3	3	3
30	7	2	0	0	0	1	0	0	0	1	1	2	1	0	1	1	4	1	1	1	1	1	1	1	615	501	0.81	371	0.6	452	0.73	476	0.77	497	0.81	547	0.89	540	0.88	1	1	1	1	2	1	1
31	23	2	0	0	0	1	0	0	0	0	0	3	1	1	1	28	1	3	3	3	3	3	3	3	463	422	0.91	514	1.11	447	0.96	519	1.12	507	1.09	480	1.03	503	1.08	2	3	3	3	3	3	3
32	23	2	0	0	0	1	0	0	0	0	0	3	1	1	1	28	3	2	2	2	2	2	3	3	501	503	1	482	0.96	241	0.48	487	0.97	508	1.01	456	0.91	459	0.91	2	2	1	2	2	3	3
33	25	2	1	0	0	0	0	0	0	6	3	1	1	1	1	4	4	1	1	0	1	1	1	0	619	434	0.7	553	0.89	160	0.25	559	0.9	380	0.61	231	0.37	138	0.22	1	2	0	1	1	1	0
34	25	2	1	0	0	0	0	0	0	6	3	1	1	1	1	4	3	2	2	1	2	1	2	1	520	552	1.06	670	1.29	306	0.59	577	1.1	371	0.71	541	1.04	450	0.86	2	2	1	2	1	2	1
35	34	1	1	0	0	1	0	0	0	1	2	2	1	1	1	75	4	2	1	1	2	2	3	3	502	612	1.22	262	0.52	356	0.71	583	1.16	559	1.11	507	1.01	510	1.02	2	1	1	2	2	3	3
36	34	1	1	0	0	1	0	0	0	1	2	2	1	1	1	75	1	3	3	3	3	3	3	3	503	516	1.02	523	1.03	497	0.98	556	1.1	574	1.14	528	1.05	522	1.04	2	3	3	3	3	3	3
37	36	1	1	0	0	0	0	0	0	0	1	1	1	1	0	64	4	2	2	1	2	2	3	3	386	386	1	407	1.05	295	0.76	464	1.2	425	1.1	429	1.11	471	1.22	2	2	1	2	2	3	3
38	36	1	1	0	0	0	0	0	0	0	1	1	1	1	0	64	1	3	3	3	2	2	3	3	400	357	0.89	554	1.38	478	1.19	447	1.12	462	1.15	462	1.15	442	1.11	2	3	3	2	2	3	3
39	28	1	1	0	0	1	0	0	0	0	0	3	1	1	1	2	2	2	2	1	2	2	3	3	577	540	0.93	642	1.11	426	0.73	553	0.96	608	1.05	667	1.2	643	1.15	2	2	1	2	2	3	3
40	28	1	1	0	0	1	0	0	0	0	0	3	1	1	1	2	2	2	2	1	2	2	3	3	530	597	1.12	561	1.05	364	0.68	567	1.07	582	1.1	677	1.28	646	1.21	2	2	1	2	2	3	3
41	15	1	1	0	0	0	0	0	0	0	0	1	1	0	1	1	2	2	2	1	3	2	3	3	632	696	1.1	697	1.1	348	0.55	822	1.3	610	0.96	645	1.02	808	1.28	2	2	1	3	3	3	3
42	15	1	1	0	0	0	0	0	0	0	0	1	1	0	1	1	1	3	3	3	3	3	3	3	652	604	0.92	683	1.04	691	1.06	719	1.1	774	1.18	795	1.22	836	1.28	2	3	3	3	3	3	3
43	11	1	1	1	0	0	0	0	0	2	2	2	1	1	0	1	2	2	3	3	2	1	3	3	532	597	1.12	766	1.44	739	1.39	782	1.46	484	0.91	709	1.33	609	1.14	2	3	3	2	1	3	3
44	11	1	1	1	0	0	0	0	0	2	2	2	1	1	0	1	4	1	1	1	2	1	2	1	514	493	0.96	433	0.84	403	0.78	581	1.13	425	0.82	576	1.12	456	0.89	1	1	1	2	1	2	1
45	25	1	0	0	1	0	0	0	0	0	1	1	2	0	0	8	2	2	2	1	2	2	3	3	572	556	0.97	556	0.97	422	0.74	535	0.94	591	1.03	545	0.95	595	1.04	2	2	1	2	2	3	3

46	25	1	0	0	1	0	0	0	0	0	1	1	2	0	0	8	0	3	3	3	3	3	3	3	565	522	0.92	600	1.06	576	1.02	576	1.02	618	1.09	564	0.99	670	1.18	2	3	3	3	3	3	3
47	50	2	0	1	0	0	0	0	0	0	0	1	2	0	0	56	2	1	2	2	2	3	3	3	475	538	1.13	387	0.81	304	0.64	494	1.04	438	0.92	555	1.16	508	1.07	2	1	1	2	2	3	3
48	50	2	0	1	0	0	0	0	0	0	0	1	2	0	0	56	1	1	1	1	2	3	3	3	470	347	0.74	316	0.67	252	0.54	391	0.83	448	0.95	506	1.07	496	1.05	1	1	1	1	2	3	3
49	35	2	1	0	0	1	0	0	0	0	0	2	1	1	1	1	2	2	2	2	1	2	3	3	545	511	0.94	556	1.02	648	1.18	414	0.75	530	0.97	582	1.06	592	1.08	2	2	2	1	2	3	3
50	35	2	1	0	0	1	0	0	0	0	0	2	1	1	1	1	3	2	2	1	1	1	3	3	518	641	1.23	513	0.99	372	0.72	385	0.74	327	0.63	513	0.99	582	1.12	2	2	1	1	1	3	3
51	38	1	0	0	0	0	1	0	0	1	1	1	1	1	0	1	4	2	1	0	1	1	1	1	512	581	1.13	296	0.57	141	0.27	232	0.45	225	0.44	275	0.54	284	0.55	2	1	0	1	1	1	1
52	38	1	0	0	0	0	1	0	0	1	1	1	1	1	0	1	4	1	1	1	1	1	3	3	589	453	0.77	365	0.62	258	0.44	230	0.39	329	0.56	572	0.97	738	1.25	1	1	1	1	1	3	3
53	37	1	1	0	0	0	0	0	1	13	4	1	1	1	0	2	3	1	1	1	3	3	3	3	241	180	0.74	188	0.78	116	0.48	393	1.63	366	1.52	368	1.52	367	1.52	1	1	1	3	3	3	3
54	37	1	1	0	0	0	0	0	1	13	4	1	1	1	0	2	0	3	3	3	3	3	3	3	243	270	1.11	422	1.73	341	1.4	390	1.6	373	1.53	394	1.62	347	1.42	2	3	3	3	3	3	3
55	11	1	1	0	0	0	0	0	0	0	2	1	1	1	0	4	4	1	1	1	1	1	1	1	499	282	0.56	277	0.56	175	0.35	230	0.46	202	0.41	165	0.33	177	0.35	1	1	1	1	1	1	1
56	11	1	1	0	0	0	0	0	0	0	2	1	1	1	0	4	4	1	1	1	1	1	2	1	490	357	0.72	273	0.55	167	0.34	220	0.44	191	0.39	590	1.2	185	0.38	1	1	1	1	1	2	1
57	25	2	1	0	1	0	0	0	0	0	0	2	1	1	1	3	3	1	1	1	1	1	3	3	546	427	0.78	499	0.91	327	0.6	422	0.77	573	1.05	522	0.96	600	1.1	1	1	1	1	2	3	3
58	25	2	1	0	1	0	0	0	0	0	0	2	1	1	1	3	3	2	2	1	2	2	3	3	552	550	0.99	578	1.05	427	0.77	551	0.99	638	1.16	544	0.98	663	1.2	2	2	1	2	2	3	3
59	37	1	1	0	1	0	0	0	0	0	1	2	1	1	1	60	0	3	3	3	3	3	3	3	571	548	0.96	549	0.96	565	0.99	502	0.88	603	1.05	525	0.92	538	0.94	2	3	3	3	3	3	3
60	37	1	1	0	1	0	0	0	0	0	1	2	1	1	1	60	4	1	1	1	3	3	3	3	465	380	0.82	449	0.96	406	0.87	558	1.2	435	0.94	512	1.1	646	1.38	1	1	1	3	3	3	3
61	4	2	1	0	0	0	0	0	0	3	1	2	1	1	0	15	3	1	1	1	1	2	3	3	610	771	1.26	584	0.95	512	0.84	403	0.66	873	1.43	778	1.27	735	1.2	2	1	1	1	2	3	3
62	4	2	1	0	0	0	0	0	0	3	1	2	1	1	0	15	4	1	0	0	1	1	2	1	518	395	0.76	136	0.26	153	0.29	404	0.78	384	0.74	712	1.37	328	0.63	1	0	0	1	1	2	1
63	12	2	1	0	0	0	0	0	0	2	2	2	1	1	0	5	4	1	1	1	1	1	1	1	513	422	0.82	418	0.81	303	0.59	495	0.96	434	0.84	460	0.89	433	0.84	1	1	1	1	1	1	1
64	12	2	1	0	0	0	0	0	0	2	2	2	1	1	0	5	2	1	1	1	1	2	3	3	471	420	0.89	304	0.64	205	0.43	696	1.47	379	0.8	575	1.22	553	1.17	1	1	1	2	1	3	3
65	7	2	1	0	0	0	0	0	0	4	2	1	1	1	0	6	1	1	2	1	1	1	3	3	570	855	1.5	970	1.7	857	1.5	560	0.98	457	0.8	675	1.18	801	1.4	2	2	2	1	1	3	3
66	7	2	1	0	0	0	0	0	0	4	2	1	1	1	0	6	4	1	1	1	1	1	1	1	501	485	0.96	416	0.83	448	0.89	490	0.98	396	0.79	315	0.63	417	0.83	1	1	1	1	1	1	1
67	31	2	0	1	0	0	0	0	0	0	0	3	1	1	1	1	3	2	1	1	1	1	3	3	533	400	0.75	428	0.8	218	0.41	367	0.69	378	0.71	563	1.06	529	0.99	1	1	1	1	1	3	3
68	31	2	0	1	0	0	0	0	0	0	0	3	1	1	1	1	2	1	2	2	1	1	3	3	526	299	0.57	565	1.07	540	1.02	438	0.83	441	0.84	537	1.02	531	1.01	1	2	2	1	1	3	3
69	23	2	1	0	0	0	0	0	0	0	0	2	1	1	1	70	0	3	3	3	3	3	3	3	556	629	1.13	634	1.14	604	1.08	606	1.09	645	1.16	658	1.18	704	1.26	2	3	3	3	3	3	3
70	23	2	1	0	0	0	0	0	0	0	0	2	1	1	1	70	3	2	1	1	3	3	3	3	522	609	1.16	473	0.9	441	0.84	545	1.04	686	1.31	741	1.41	653	1.25	2	1	1	3	3	3	3
71	7	2	0	1	0	0	0	0	0	0	0	1	1	1	0	3	4	1	1	1	1	1	1	1	441	455	1.03	303	0.68	233	0.53	425	0.96	442	1	263	0.59	249	0.56	1	1	1	1	1	1	1
72	7	2	0	1	0	0	0	0	0	0	0	1	1	1	0	3	1	1	3	3	1	1	2	2	427	287	0.67	429	1.01	440	1.03	387	0.91	389	0.91	582	1.36	597	1.4	1	3	3	1	1	2	2
73	4	2	1	0	0	0	0	0	0	2	2	3	1	1	0	2	3	2	1	1	1	2	3	3	504	586	1.16	469	0.93	371	0.74	414	0.82	657	1.3	530	1.05	676	1.34	2	1	1	1	2	3	3
74	4	2	1	0	0	0	0	0	0	2	2	3	1	1	0	2	3	2	1	1	1	2	3	3	450	616	1.37	487	1.08	380	0.84	431	0.96	374	0.83	513	1.14	544	1.21	2	1	1	1	1	3	3
75	23	2	1	0	0	0	0	0	0	0	0	1	1	1	0	88	3	2	2	1	2	1	3	3	586	560	0.95	622	1.06	255	0.43	598	1.02	338	0.56	533	0.91	640	1.09	2	2	1	2	1	3	3
76	11	2	1	0	0	0	0	0	0	0	0	3	1	1	1	31	4	1	2	1	1	1	3	3	508	512	1.01	599	1.17	312	0.61	395	0.78	387	0.76	575	1.13	563	1.11	2	2	1	1	1	3	3
77	3	1	1	1	0	0	0	0	0	4	3	3	1	1	1	6	4	1	1	1	1	1	3	3	686	563	0.82	546	0.79	384	0.56	470	0.68	465	0.68	972	1.41	900	1.31	1	1	1	1	1	3	3
78	3	2	1	1	1	0	0	1	0	0	1	3	1	1	1	7	4	1	2	1	1	1	2	1	524	462	0.88	536	1.02	358	0.68	487	0.93	401	0.76	569	1.08	386	0.73	1	2	1	1	1	2	1
79	12	2	1	0	1	0	0	0	0	0	0	3	1	1	0	1	3	2	1	1	2	2	3	3																2	2	2	2	1	3	3
80	12	2	1	0	1	0	0	0	0	0	0	3	1	1	0	1	4	2	2	1	1	1	3	3																2	2	1	2	1	3	3
81	8	1	1	0	1	0	0	0	0	1	2	3	1	1	1	1	4	1	1	1	1	1	1	1																1	1	1	1	1	1	1
82	8	1	1	0	1	0	0	0	0	1	2	3	1	1	1	1	4	1	1	1	1	1	1	1																1	1	1	1	1	1	1
83	50	1	0	0	0	1	0	0	0	0	0	3	1	1	1	1	3	1	1	1	1	1	3	3																1	1	1	1	1	3	3
84	50	1	0	0	0	1	0	0	0	0	0	3	1	1	1	1	3	1	1	1	1	1	3	3																1	1	1	1	1	3	3
85	27	1	1	0	0	0	0	0	0	0	0	2	1	1	1	31	0	3	3	3	3	3	3	3																2	3	3	3	3	3	3
86	27	1	1	0	0	0	0	0	0	0	0	2	1	1	1	31	4	2	1	1	3	3	1	1																2	1	1	3	3	1	1
87	30	1	1	0	0	0	0	0	0	0	1	2	1	1	0	1	0	3	3	3	3	3	3	3																2	3	3	3	3	3	3
88	30	1	1	0	0	0	0	0	0	0	1	2	1	1	0	1	2	1	3	1	3	3	3	3																1	3	1	3	3	3	3

APPENDIX D - INFORMED CONSENT FORM

Title of Study:

Perfusion Patterns In Varying Angiographic Stages Of Indian Moyamoya Patients

Principal Investigator:
Dr. S M Krishna Mohan M, Senior Resident, Department of Neurology, SCTIMST

Co-Principal Investigator:
Dr. Sajith S, Professor, Department of Neurology, SCTIMST

Please tick the following points:

I agree to participate as a participant in the study described in the Participant Information Sheet attached to this form.	[ ]
I acknowledge that I have read the Participant Information Sheet, which explains why I have been selected, the aims of the study and the nature and the possible risks of the investigation, and the information sheet has been explained to me to my satisfaction.	[ ]
Before signing this consent form, I have been given the opportunity of asking any questions relating to any possible physical and mental harm I might suffer as a result of my participation and I have received satisfactory answers.	[ ]
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	[ ]
I agree that research data gathered from the results of the study may be published, provided that I cannot be identified.	[ ]
I understand that if I have any questions relating to my participation in this research, I may contact my doctor, who will be happy to answer them.	[ ]
I acknowledge receipt of a copy of this Consent Form and the Participant Information Sheet attached to this form	[ ]

Name of Participant

Signature of Participant Date

Name of Caretaker or Next of Kin

(If patient not directly consented)

Relationship with the patient

Signature of Caretaker or Next of Kin Date

Name of Witness

Signature of Witness Date

Name of Person conducting Informed Consent discussion

Signature of Person conducting Informed Consent discussion Date

APPENDIX D – INFORMED CONSENT FORM IN MALAYALAM

ശ്രീചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ് ആന്റ് ടെക്നോളജി,
തിരുവനന്തപുരം, കേരളം 695011

മസ്തിഷ്ക്കാഘാത പരിചരണത്തിനായുള്ള സമഗ്ര പരിപാടി

രോഗിക്കുള്ള കാര്യവിവരണപത്രം

പഠനശീർഷകം

ഇൻഡ്യയിലെ മൊയമൊയ രോഗികളിൽ നടത്തുന്ന ആൻജിയോഗ്രഫിയുടെ വ്യത്യസ്ത ഘട്ടങ്ങളിൽ രക്തചംക്രമണവ്യവസ്ഥയിലെ ദ്രാവകങ്ങളുടെ പ്രയാണത്തിന്റെ മാതൃകകളും (പെർഫ്യൂഷൻ).

പ്രധാന ഗവേഷകൻ

ഡോ. എസ് എം കൃഷ്ണ മോഹൻ എം, സീനിയർ റസിഡന്റ്, ഡിപ്പാർട്ട്മെന്റ് ഓഫ് ന്യൂറോളജി, SCTIMST

സഹപ്രധാനഗവേഷകൻ

ഡോ. സജിത് എസ്, പ്രൊഫസർ, ഡിപ്പാർട്ട്മെന്റ് ഓഫ് ന്യൂറോളജി, SCTIMST

(താഴെപ്പറയുന്നവയിൽ ദയവായി ടിക് ചെയ്യുക)

(i) ഈ പത്രികയോടൊപ്പമുള്ള, പങ്കെടുക്കുന്നവർക്കുള്ള കാര്യവിവരണപത്രത്തിൽ വിശദീകരിക്കുന്ന പഠനത്തിൽ പങ്കെടുക്കാൻ ഞാൻ സമ്മതിക്കുന്നു.	[ ]
(ii) എന്നെ എന്തുകൊണ്ട് തിരഞ്ഞെടുത്തു, പഠനത്തിന്റെ ഉദ്ദേശം, സ്വഭാവം, പരിശോധനയിൽ ഉണ്ടാവാനിടയുള്ള അപായങ്ങൾ എന്നിവ വിവരിക്കുന്ന പങ്കെടുക്കുന്നവർക്കുള്ള കാര്യവിവരണപത്രം വായിച്ചതായും എന്റെ തൃപ്തിയ്ക്കനുസരിച്ച് വിശദീകരിച്ചുതന്നതായും ഞാൻ സമ്മതിക്കുന്നു.	[ ]
(iii) സമ്മതപത്രത്തിൽ ഒപ്പു വയ്ക്കുന്നതിനുമുമ്പ്, ഈ പഠനത്തിൽ പങ്കെടുക്കുന്നതുകൊണ്ട് ശാരീരികവും മാനസികവുമായ എന്തെങ്കിലും ഹാനി എനിക്ക് ഉണ്ടാകാൻ സാദ്ധ്യതയുണ്ടോ എന്നതുമായി ബന്ധപ്പെട്ട ചോദ്യങ്ങൾ ചോദിക്കാൻ എനിക്ക് അവസരം ഉണ്ടാവുകയും തൃപ്തികരമായ മറുപടി ലഭിക്കുകയും ചെയ്തു	[ ]
(iv) എന്റെ പങ്കാളിത്തം സ്വമേധയായാണെന്നും, കാരണമൊന്നും നൽകാതെയും എന്റെ വൈദ്യപരിചരണത്തെയും നിയമപരമായഅവകാശങ്ങളെയും ബാധിക്കാതെ ഏതു സമയത്തും എനിക്ക് പിൻമാറാൻ സ്വാതന്ത്ര്യമുണ്ടെന്നും മനസ്സിലാക്കുന്നു.	[ ]
(v) പഠനഫലമായി ശേഖരിച്ച വിവരങ്ങൾ പ്രസിദ്ധീകരിക്കുമ്പോൾ എന്നെ തിരിച്ചറിയാനിടയാകുന്നതൊന്നും വെളിപ്പെടുത്തുകയില്ലെന്ന് ഞാൻ മനസ്സിലാക്കുന്നു.	[ ]
(vi) ഗവേഷണത്തിൽ പങ്കെടുക്കുന്നതുമായി ബന്ധപ്പെട്ട് എനിക്ക് ചോദ്യങ്ങളുണ്ടെങ്കിൽ എനിക്ക് ഡോക്ടറെ ബന്ധപ്പെടാമെന്നും ഉത്തരം തരുന്നതിൽ അദ്ദേഹത്തിന് സന്തോഷമേയുള്ളൂവെന്നും ഞാൻ മനസ്സിലാക്കുന്നു.	[ ]
(vii) ഈ പത്രികയോടൊപ്പം നൽകിയിട്ടുള്ള പങ്കാളികൾക്കുള്ള വിവരണപത്രവും സമ്മതപത്രവും കിട്ടിയതായി ഞാൻ അറിയിക്കുന്നു.	[ ]

പങ്കെടുക്കുന്നയാളുടെ പേര്

പങ്കെടുക്കുന്നയാളുടെ ഒപ്പ് തീയതി സമയം

പരിചരിക്കുന്നയാളുടെ അല്ലെങ്കിൽ അടുത്തബന്ധുവിന്റെ പേര്
(രോഗി നേരിട്ടല്ല സമ്മതം തരുന്നതെങ്കിൽ)

രോഗിയുമായുള്ള ബന്ധം

പരിചരിക്കുന്നയാളുടെ അല്ലെങ്കിൽ അടുത്തബന്ധുവിന്റെ ഒപ്പ് തീയതി സമയം

സാക്ഷിയുടെ പേര്

സാക്ഷിയുടെ ഒപ്പ് തീയതി സമയം

സമ്മതപത്രത്തെപ്പറ്റി ചർച്ച ചെയ്തയാളുടെ പേര്

സമ്മതപത്രത്തെപ്പറ്റി ചർച്ച ചെയ്തയാളുടെ ഒപ്പ് തീയതി സമയം

APPENDIX D- PATIENT INFORMATION SHEET

Title of the study:

Perfusion Patterns In Varying Angiographic Stages Of Indian Moyamoya Patients

Principal Investigator:

Dr. S M Krishna Mohan M, Senior Resident, Department of Neurology, SCTIMST

Co-Principal Investigator:

Dr. Sajith . S., Professor, Department of Neurology, SCTIMST

Sir/ Madam,

We invite you to take part in our study titled *"PERFUSION PATTERNS IN VARYING ANGIOGRAPHIC STAGES OF INDIAN MOYAMOYA PATIENTS"* an observational study. Before you agree to participate in this research study, it is important that you read and understand this information sheet which will provide you with all the information needed for participation in this study so that you can make a well informed and considered decision about participation. In addition, should you have any questions, the investigator and his team members will be happy to answer them and explain to you more about this research study, the procedure involved and the related issues. You may ask them any questions you may have regarding the study, or ask them to explain any word or information that you don't clearly understand.

Study Overview

You are invited to take part in this study as you have stenosis in one of the major blood vessels supplying the brain called Moyamoya disease. As part of investigative workup, a procedure

called DSA is done to stage the severity of the disease. A special MR sequence called ASL is also done and will give more information of the perfusion pattern and the severity of the disease. Patients diagnosed with MMD who are admitted in Comprehensive stroke care centre, Department of Neurology, SCTIMST will be included in the study.

Purpose of this study

The purpose of this study is to evaluate perfusion patterns in patients with MMD and to compare the perfusion patterns in different angiographic stages of MMD

Study Procedures

If you are willing to participate, you will be interviewed and examined by neurologist and the clinical findings will be noted. This shall be planned when you are admitted for evaluation or revascularisation surgery. As a part of your management plan you will have to undergo MRI brain including ASL sequence and DSA as per standard protocol, data of which will be used in this study.

Risks and Discomfort

This study involves only a structured interview by neurologist along with MR imaging and DSA done as part of standard management protocol. There are no additional risks or costs associated with the study.

Benefits

Taking part in this research study may not benefit you. However, we do hope that this study will shed light whether the natural history of the MMD and its various stages demonstrated by

DSA follows expected perfusion patterns on MR ASL imaging modality. Thus help in better understanding of the MMD and formulating better care in the future.

Confidentiality

Your privacy is very important to us and the results of the tests performed on you will be treated as highly confidential, and nobody other than the investigators listed above will be knowing the test results. Your name or any other identifiable details will not be published in any research paper or scientific presentation arising out of the study.

Rights

Your participation in the trial is voluntary. You do not have to take part in this study if you are unwilling and you will not be losing any of your rights as a patient if you choose not to participate. You will also be at the liberty to withdraw from the study at any stage (even after signing this consent form) of the study in case you want to withdraw.

Contact Information

- When you read this information, your treating doctor will be available to discuss and answer any questions you may have. If you have any queries please contact:

  Dr S M Krishna Mohan M

  Senior Resident, Department of Neurology,

  Sree Chitra Tirunal Institute for Medical Sciences and Technology

  Tel: +91 8985885589, Email: kmrmc08msm@sctimst.ac.in

- If you have any questions, concerns or complaints about the research please contact:

  Dr. Srinivas G

  Member Secretary, Institutional Ethics Committee,

  Sree Chitra Tirunal Institute for Medical Sciences and Technology

  Tel: 0471- 2524689, Email: iec.mem.sec@sctimst.ac.in

APPENDIX D- PATIENT INFORMATION SHEET IN MALAYALAM

ശ്രീചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ് ആന്റ്
ടെക്നോളജി, തിരുവനന്തപുരം, കേരളം 695011

മസ്തിഷ്ക്കാഘാത പരിചരണത്തിനായുള്ള സമഗ്ര പരിപാടി

രോഗിക്കുള്ള കാര്യവിവരണപത്രം

പഠനശീർഷകം
ഇൻഡ്യയിലെ മൊയമൊയ രോഗികളിൽ നടത്തുന്ന ആൻജിയോഗ്രഫിയുടെ വ്യത്യസ്ത ഘട്ടങ്ങളിൽ രക്തചംക്രമണവ്യവസ്ഥയിലെ ദ്രാവകങ്ങളുടെ പ്രയാണത്തിന്റെ മാതൃകകളും (പെർഫ്യൂഷൻ).

പ്രധാന ഗവേഷകൻ
ഡോ. എസ് എം കൃഷ്ണ മോഹൻ എം, സീനിയർ റസിഡന്റ്, ഡിപ്പാർട്ട്മെന്റ് ഓഫ് ന്യൂറോളജി, SCTIMST

സഹപ്രധാനഗവേഷകൻ
ഡോ. സജിത് എസ്, പ്രൊഫസർ, ഡിപ്പാർട്ട്മെന്റ് ഓഫ് ന്യൂറോളജി, SCTIMST

ശ്രീ/ശ്രീമതി,

ഇൻഡ്യയിലെ മൊയമൊയ രോഗികളിൽ നടത്തുന്ന ആൻജിയോഗ്രഫിയുടെ വ്യത്യസ്ത ഘട്ടങ്ങളിൽ രക്തചംക്രമണവ്യവസ്ഥയിലെ ദ്രാവകങ്ങളുടെ പ്രയാണത്തിന്റെ മാതൃകകളും (പെർഫ്യൂഷൻ) എന്ന നിരീക്ഷണ പഠനത്തിൽ പങ്കെടുക്കാവാൻ താങ്കളെ ഞങ്ങൾ ക്ഷണിക്കുന്നു. താങ്കൾ പഠനത്തിൽ പങ്കെടുക്കാൻ സമ്മതിക്കുന്നതിനു മുമ്പ്, ഈ പഠനത്തിൽ പങ്കെടുക്കാനാവശ്യമായ വിവരങ്ങൾ നൽകുന്ന കാര്യവിവരണപത്രം വായിക്കുകയും മനസ്സിലാക്കുകയും ചെയ്യേണ്ടുന്നത് കാര്യബോധത്തോടെയും വേണ്ടുന്ന പരിഗണനയോടെയുമുള്ള തീരുമാനമെടുക്കുന്നതിന് പ്രധാനമാണ്. കൂടാതെ താങ്കൾക്കെന്തെങ്കിലും ചോദ്യങ്ങളുണ്ടെങ്കിൽ, അവയ്ക്കുത്തരം നൽകാനും താങ്കളോട് ഈ ഗവേഷണ പഠനം, ഉള്ളടങ്ങുന്ന നടപടികൾ, ബന്ധപ്പെട്ട പ്രശ്നങ്ങൾ എന്നിവയെപ്പറ്റി കൂടുതൽ വിശദീകരിക്കാനും ഗവേഷകനും സംഘാംഗങ്ങൾക്കും സന്തോഷമേയുള്ളു. ഈ പഠനസംബന്ധമായി താങ്കൾക്ക് ഏത് ചോദ്യവും ചോദിക്കാം, താങ്കൾക്ക് വ്യക്തമായി മനസ്സിലാകാത്ത ഏത് വാക്കിനെപ്പറ്റിയും വിവരത്തെപ്പറ്റിയും വിശദീകരിക്കാനാവശ്യപ്പെടാം.

പഠനസംബന്ധമായ പൊതു അവലോകനം
താങ്കളുടെ തലച്ചോറിലേയ്ക്ക് രക്തം നൽകുന്ന പ്രധാന രക്തക്കുഴലുകളിലൊന്ന് സങ്കോചിക്കുന്ന മൊയമൊയ എന്നറിയപ്പെടുന്ന രോഗം ഉള്ളതിനാലാണ് ഈ പഠനത്തിൽ പങ്കെടുക്കാൻ താങ്കളെ ഞങ്ങൾ ക്ഷണിക്കുന്നത്. രോഗത്തിന്റെ ഗുരുതരാവസ്ഥ വിലയിരുത്താനുള്ള പരിശോധനയുടെ ഭാഗമായി ഡിഎസ്എ എന്ന നടപടി ചെയ്യും. പെർഫ്യൂഷൻ മാതൃകയെപ്പറ്റിയും, രോഗത്തിന്റെ തീവ്രതയെപ്പറ്റിയും കൂടുതലറിയാൻ സഹായകമായ എഎസ്എൽ എന്നറിയപ്പെടുന്ന ഒരു പ്രത്യേക എംആർ പരമ്പരയും ചെയ്യും. മൊയാമൊയാ രോഗം നിർണ്ണിക്കപ്പെട്ട, SCTIMST ന്യൂറോളജി വിഭാഗത്തിലെ മസ്തിഷ്ക്കാഘാത സമഗ്ര പരിചരണ കേന്ദ്രത്തിൽ പ്രവേശിപ്പിക്കപ്പെട്ട രോഗികളെ ഈ പഠനത്തിൽ ഉൾപ്പെടുത്തും.

പഠനത്തിന്റെ ഉദ്ദേശം
മൊയമൊയ രോഗികളിലെ പെർഫ്യൂഷന്റെ സ്വഭാവങ്ങളും ആൻജിയോഗ്രഫിയുടെ വ്യത്യസ്ത ഘട്ടങ്ങളിലെ പെർഫ്യൂഷന്റെ മാതൃകകളും തമ്മിൽ താരതമ്യം ചെയ്യുക എന്നതാണ് ഈ പഠനത്തിന്റെ ഉദ്ദേശം.

പഠന സംബന്ധമായ നടപടികൾ

താങ്കൾ പങ്കെടുക്കാൻ സമ്മതിക്കുകയാണെങ്കിൽ, ഒരു ന്യൂറോളജിസ്റ്റ് താങ്കളുമായി അഭിമുഖം നടത്തുകയും കൂടാതെ താങ്കളെ പരിശോധിക്കുകയും ക്ലിനിക്കൽ കണ്ടെത്തലുകൾ രേഖപ്പെടുത്തുകയും ചെയ്യും. വിലയിരുത്തലിനോ രക്തപ്രവാഹം പുനസ്ഥാപിക്കാനുള്ള ശസ്ത്രക്രിയയ്ക്കോ ആയി താങ്കളെ ആശുപത്രിയിൽ പ്രവേശിപ്പിക്കുമ്പോൾ തന്നെ ഇത് ആസൂത്രണം ചെയ്യുന്നതാണ്. താങ്കളുടെ ചികിത്സയുടെ അംഗീകൃത നടപടിക്രമങ്ങളുടെ ഭാഗമായ എഎസ്എൽ പരമ്പര ഉൾപ്പെടെയുള്ള തലച്ചോറിന്റെ എംആർഐയുകളും ഡിഎസ് എയും താങ്കൾ വിധേയമാകണം, ഈ പരിശോധനകളിൽ നിന്നും ലഭിക്കുന്ന വിവരങ്ങൾ ഈ പഠനത്തിനായി ഉപയോഗിക്കും. ,

അപകടസാദ്ധ്യതകളും അസൗകര്യങ്ങളും

ഈ പഠനത്തിൽ ന്യൂറോളജിസ്റ്റ് നടത്തുന്ന സുഘടിതമായ ഒരു അഭിമുഖവും ടികിത്സയുടെ അംഗീകൃത നടപടിക്രമമായ എംആർഐയും ഡിഎസ്എയുമേ ഉൾപ്പെടുന്നുള്ളു. ഈ പഠനവുമായി ബന്ധപ്പെട്ട് കൂടുതലായി അപകടങ്ങളൊ ചിലവോ ഇല്ല.

നേട്ടങ്ങൾ

ഈ പഠനത്തിൽ പങ്കെടുക്കുന്നതുകൊണ്ട് താങ്കൾക്ക് നേട്ടമൊന്നുമുണ്ടായേക്കില്ല. എന്നിരുന്നാലും, മൊയമൊയയുടെ സ്വാഭാവികചരിത്രവും ഡിഎസ്എയിൽ പ്രകടമാകുന്ന അതിന്റെ വ്യത്യസ്ത ഘട്ടങ്ങളും, എംആർ എഎസ്എൽ ഇമേജിംഗ് സമ്പ്രദായത്തിൽ പ്രതീക്ഷിച്ച പെർഫ്യൂഷൻ മാതൃകകൾക്ക് അനുസൃതമോ എന്നതിൽ വെളിച്ചം വീശാൻ ഈ പഠനം സഹായകമാകുമെന്ന് ഞങ്ങൾ പ്രതീക്ഷിക്കുന്നു. അങ്ങനെ മൊയമൊയയെപ്പറ്റി മെച്ചപ്പെട്ട ധാരണയുണ്ടാക്കാനും തീരുമാനമെടുക്കാനും ഈ പഠനം സഹായകമായേക്കാമെന്ന് ഞങ്ങൾ പ്രതീക്ഷിക്കുന്നു.

രഹസ്യാത്മകത

താങ്കളുടെ സ്വകാര്യത ഞങ്ങൾക്ക് പ്രധാനമാകയാൽ താങ്കളിൽ നടത്തിയ പരിശോധനകളുടെ ഫലങ്ങൾ വളരെ രഹസ്യമായിരിക്കും, മുകളിൽ പറഞ്ഞ ഗവേഷകർ ഒഴികെ മറ്റാർക്കും പരിശോധനാഫലങ്ങൾ അറിയുകയില്ല. ഈ പഠനഫലമായി ഉണ്ടാകുന്ന ഗവേഷണ പ്രസിദ്ധീകരണത്തിലോ ശാസ്ത്ര പ്രദർശനത്തിലോ താങ്കളുടെ പേരോ തിരിച്ചറിയാനിടയാക്കുന്ന മറ്റേതെങ്കിലും വിശദാംശങ്ങളോ പ്രസിദ്ധീകരിക്കുകയുമില്ല.

അവകാശങ്ങൾ

ഈ പരീക്ഷണത്തിലെ താങ്കളുടെ പങ്കാളിത്തം സ്വമേധയായാണ്. താങ്കൾക്ക് സമ്മതമില്ലെങ്കിൽ ഈ പഠനത്തിൽ പങ്കെടുക്കേണ്ടതില്ല, പങ്കെടുക്കുന്നില്ലെന്ന് തീരുമാനിച്ചാലും രോഗിയെന്ന നിലയിലുള്ള താങ്കളുടെ അവകാശങ്ങളൊന്നും നഷ്ടപ്പെടില്ല. പഠനത്തിന്റെ ഏത് ഘട്ടത്തിലും (സമ്മതപത്രം ഒപ്പിട്ടശേഷവും) താങ്കൾക്ക് പഠനത്തിൽ നിന്നും പിൻമാറാവുന്നതാണ്.

ബന്ധപ്പെടാനുള്ള വിവരങ്ങൾ

- താങ്കൾ ഈ വിവരങ്ങൾ വായിക്കുമ്പോൾ ചർച്ചചെയ്യാനും താങ്കൾക്കുണ്ടായേക്കാവുന്ന ചോദ്യങ്ങൾക്ക് ഉത്തരങ്ങൾ നൽകാനും താങ്കളെ ചികിത്സിക്കുന്ന ഡോക്ടർ ഉണ്ടാവും. താങ്കൾക്കെന്തെങ്കിലും ചോദ്യങ്ങളുണ്ടെങ്കിൽ ദയവായി ബന്ധപ്പെടുക

ഡോ. എസ് എം കൃഷ്ണ മോഹൻ എം, സീനിയർ റെസിഡന്റ്, ന്യൂറോളജി ഡിപ്പാർട്ട്മെന്റ്,
ശ്രീ ചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ് ആന്റ് ടെക്നോളജി
ഫോൺ 91 8985885589, ഇമെയിൽ: kmrmc08msm@sctimst.ac.in

ഗവേഷണത്തെപ്പറ്റി താങ്കൾക്ക് ചോദ്യങ്ങൾ, ഉത്കണ്ഠ അല്ലെങ്കിൽ പരാതി എന്നിവയുണ്ടെങ്കിൽ ദയവായി ബന്ധപ്പെടുക:

ഡോ. ശ്രീനിവാസ് ജി, മെമ്പർ സെക്രട്ടറി, ഇൻസ്റ്റിറ്റ്യൂഷണൽ എത്തിക്സ് കമ്മിറ്റി
ശ്രീ ചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ് ആന്റ് ടെക്നോളജി

APPENDIX E– PLAGIARISM CERTIFICATE