ASSESSMENT OF NEURONAL PLASTICITY IN ARTERIOVENOUS MALFORMATIONS (AVM) WITH OVERLAP ON ELOQUENT AREAS CORRELATION BETWEEN LOCATION ON MRI AND PRE AND POSTOPERATIVE NEUROLOGICAL DEFICIT

DISSERTATION SUBMITTED FOR THE PARTIAL FULFILMENT

FOR THE REQUIREMENT OF THE DEGREE OF

M.CH NEUROSURGERY

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DECLARATION

This thesis titled "ASSESSMENT OF NEURONAL PLASTICITY IN ARTERIOVENOUS MALFORMATIONS (AVM) WITH OVERLAP ON ELOQUENT AREAS CORRELATION BETWEEN LOCATION ON MRI AND PRE AND POSTOPERATIVE NEUROLOGICAL DEFICIT." is a consolidated report based on a bonafide study of the period from 1st August 2019 to 31st July 2021, done by me under the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram.

This thesis is submitted to SCTIMST in partial fulfilment of rules and regulations of MCh Neurosurgery examination.

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CERTIFICATE

This is to certify that the thesis entitled — **Assessment of neuronal plasticity in arteriovenous malformations (AVM) with overlap on eloquent areas correlation between location on MRI and pre and postoperative neurological deficit** is a bonafide work of Dr. **Harshavardhan P Biradar** and was conducted in the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram (SCTIMST), under my guidance and supervision.

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ABBREVIATIONS

1. AVM - Arteriovenous Malformations
2. POD - Post Operative Day
3. MRI - Magnetic Resonance Imaging
4. DSA - Digital Substraction Angiography
5. SPSS - Statistical Package for Social Sciences
6. GKS – Gama Knife Surgery
7. RT – Radiotherapy

TABLE CONTENTS

SYNOPSIS

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Title [Project Title]

ASSESSMENT OF NEURONAL PLASTICITY IN ARTERIOVENOUS MALFORMATIONS (AVM) WITH OVERLAP ON ELOQUENT AREAS CORRELATION BETWEEN LOCATION ON MRI AND PRE AND POSTOPERATIVE NEUROLOGICAL DEFICIT.

Aims and objective: To assess the pre-operative and post-operative neurological deficit in operated cases of cerebral AVM, located on eloquent area on MRI.

Methodology: The present study was a prospective study, including all the patients who underwent surgery for cerebral AVM located on eloquent areas on MRI in the department of neurosurgery, SCTIMST. Patient will undergo Cerebral Angiography to asses size of AVM, Arterial supply and to know venous drainage. After surgery patient will be reassessed clinically for any neurological deficits secondary to excision of AVM. All cases of AVM located in eloquent area irrespective of grade, operated in SCTIMST under department of Neurosurgery will be included in study. AVMs located in non-eloquent areas. Bled AVM presenting in acute condition will be excluded from the study. The patient's status will be assessed preoperatively, on POD-2, POD-3 and at follow up at 3 months. Post-operative neurological deficit on follow up at 3 months will be used as simplified outcome measure.

Results: A total of 13 patients were included in this study. All were unbled. Immediate Post-operative period 6 out of 13 patients had deficits. On long Term follow up of 3 months all had recovered from their deficits. Patients with right sided AVM had better IQ compared to left sided AVM which was statistically significant (p value <0.05). Patients with left sided AVM had improvement in IQ post-operatively which was not stastically significant. Most patients with head had recovered post surgery. Two out of three patient had complete recovery from seizure and were medication free and one patient had good control with medication.

Conclusion- Patients with AVM located on eloquent area of brain had early post-operative deficits probably due to post surgery edema all but had recoverd completely on long term follow at 3 months. In an experienced surgeon AVM located on eloquent area of brain can be safely resected with good outcome on long term follow.

INTRODUCTION

INTRODUCTION

Arteriovenous malformations (AVMs) of the brain are one of the most difficult diseases to manage. The benign defect of the cerebral circulation threatens the patient with epileptic seizures, neurological deficit, and most importantly bleeding that may even be fatal. Today, the therapy of this complex disease is multidisciplinary, and specialties participating in therapy include micro neurosurgery, interventional neuroradiology and stereotactic radiosurgery. All three specialties have their advantages and complications, each of them individually as well as in combination may bring a complete cure to many patients, and can also fail altogether. Even today, a percentage of arteriovenous malformations defy any therapy, the combined forces of all three specialties may not be enough to find a solution in some cases. Thus, observation alone became a legitimate policy and recently this is chosen for the majority of Spetzler–Martin Grade IV and V where the risks of treatment outweigh the natural course of the disease.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

HISTORY

Presumably the first mention of AVM may be found in the Ebers Papyrus (dating back to approximately 1550 BC) containing descriptions of haemorrhoids, varicose veins and aneurysms. Malformations of the vessels were known both in the Roman and Arabic worlds. The first to have known and operated an extracranial AVM in European medicine was Hunter in the eighteenth century, but the first description of the pathological anatomy of AVM originated with Virchow in 1863. The first clinical diagnosis is ascribed to Steinhal who diagnosed it in 1895[1].

The first surgery of an intracranial AVM is credited to Giordano in 1889 who carried out a ligature of the supplying artery on the surface of parietal lobe. In May of the same year, however, a whole AVM was resected by Péan in Paris. These interventions still pre-dated the introduction of angiography by E. Monitz in 1927 when Cushing and Bailey published their experience, as did also Dandy at the same time[1]. The period preceding the era of microneurosurgery is associated with the names of Olivercrona and Norlén. Kunc was also the first who declared clearly in 1967 that the radical removal of an AVM was the only effective treatment[2,3].

The present may be dated as starting in 1967 when Yasargil used a microscope for the first time, adding bipolar coagulation and automatic retractors. Later, other leading personalities in the surgery of AVM became Drake, Wilson, Stein, Spetzler, Batjer, Sugita, Morgan, Lawton and many others.

INCIDENCE

The incidence rate of newly diagnosed AVMs is approximately 1 per 100,000 persons per year in industrialized societies, varying from 0.89 to 1.34 per 100,000 person-years in different population-based studies[4]. AVMs account only for 1–2% of

all strokes and 4% of all non-traumatic intracerebral haemorrhages. their unique age distribution among stroke etiologies, AVMs are responsible for one third of hemorrhagic strokes in young adults [4.] AVMs seem to be slightly more prevalent in men than women. Male:female ratios in different study populations include 1.22 in a large, international multicenter study[5].

PRESENTATION

Cerebral AVMs may go entirely unnoticed, or they may present with neurological symptoms, such as headache, focal neurological deficits, epileptic seizures or intracerebral hemorrhage with decreased levels of consciousness or death. The objective of the subsequent chapter is to outline the various mechanisms of clinical AVM presentation, and their frequency in a given patient population. Due to widespread availability of advanced cranial imaging such as MRI, more and more cerebral AVMs are found incidentally in the western and in many Asian and other countries[6].

Table 1- Presentation mode of cerebral and cerebellar AVMs in the respective literature

Presentation	Percentage
Incidentally found	10–20
Focal neurological deficit	<10
Epileptic seizures	10–40
Intracerebral and intracerebellar hemorrhage (rarely: SAH)	40–50

GRADING

There were several proposed grading systems for pial arteriovenous malformations. Most of the classifications are based on a sole nidus diameter, angioarchitecture and/or location. Later, patient's characteristics and clinical status were further considered for grading. The first classification system was suggested by Luessenhop and Genarelli in 1977[7].

The most commonly used grading system is that proposed by Spetzler and Martin (S-M grading) in 1986. This grading system evaluates the diameter of the AVM nidus, the eloquence of adjacent brain tissue and the presence or absence of deep venous drainage[8].

Table 2- Spetzler-Martin AVM grading system

Parameter Points		Points
Nidus diameter		
	<3 cm	1
	3–6 cm	2
	>6 cm	3
Deep venous drainage		
	No	0
	Yes	1
Eloquence of adjacent brain		
	No	0
	Yes	1

Lawton et al. published an AVM supplementary grading system (Lawton-Young grading system)[9]. This system considered cahracteristics like age, compactness and haemorrhagic/ non-haemorrhagic at presentation. The Spetzler-Martin supplemented system published by Lawton et al was validated in 2015 on a multicentre cohort of 1009 patients[10].

Table 3- Lawton-Young supplementary grading system

Parameter		Points
Age (Years)		
	<20	1
	20-40	2
	>40	3
Diffuse Nidus		
	No	0
	Yes	1
Unruptured Presentation		
	No	0
	Yes	1

DIAGNOSTIC IMAGING

AVMs are abnormal connections between arteries and veins resulting in arteriovenous shunting with an intervening network of vessels within the brain parenchyma and lack of a true capillary bed. The transition between arteries and veins can take place via the nidus or can be direct (fistulous) without any intervening capillary network [11]. The nidus is a tangle of abnormal vessels located in the brain parenchyma, replaces the normal arterioles and capillaries with a low resistance high flow vascular bed.

Two subtypes can be encountered[12].

a) Compact type, which consists of abnormal vessels without interspersed normal brain tissue.
b) Diffuse type in which normal brain parenchyma is interspersed throughout the tangle of vessels.

The diagnostic criteria of brain AVM include [12]

a) the presence of a nidus and
b) early venous drainage.

Computed tomography (CT):

CT findings of patent AVMs include curvilinear isodense or slightly hyperdense vascular structures that enhance strongly after intravenous contrast administration. CT scans are extremely sensitive to demonstrate acute cerebral hematoma from AVMs.

Magnetic resonance imaging (MRI):

MRI findings in AVMs depend on the flow rate and direction in feeding arteries and draining veins, the presence of acute or chronic haemorrhage and secondary abnormalities in the brain parenchyma. On standard spin-echo (SE) imaging it is

depicted a tangle of round, linear or serpentine low signal areas (flow voids) on both T1- and T2-weighted sequences representing dilated vascular structures. MRI is superior for delineating subacute or chronic haemorrhage, as well as secondary changes in the adjacent brain parenchyma such as perilesional gliosis, mass effect, and edema. Magnetic resonance angiography (MRA) sequences have been demonstrated to be of value in providing three dimensional angiographic images of AVMs. Time-of-flight (TOF) MRA technique is frequently one of the first examinations obtained for AVM evaluation in addition to conventional MRI.

Digital subtraction angiography (DSA):

Despite improvements in cross-sectional imaging, conventional DSA remains the gold standard for detailed evaluation of cerebral AVMs. Examination should provide detailed information regarding

a) Feeding arteries and associated flow-related angiopathic changes,

b) Gross evaluation of the nidus; size, hemodynamic properties, anatomic characteristics like fistulae, intranidal aneurysms, and

c) Delineation of the venous drainage into deep or superficial and signs of high-flow venous angiopathy like stenotic changes, ectasia.

Superselective angiographic studies can delineate internal angioarchitecture of AVMs.

Imaging have several roles and goals[12]:

(a) To establish the diagnosis of brain AVM in various clinical situations

(b) To make pre-therapeutic evaluation

(c) To perform post-therapeutic evaluation

The diagnostic criteria include[12]:

1.Presence of a nidus identified at either cross-sectional imaging (computed tomography, magnetic resonance imaging) or conventional angiography.

2.Early venous drainage, which is seen on dynamic studies, the gold standard being catheter angiography.

Features of the AVM to be evaluated include[13,14]:

(a) Complete identification of the arterial supply

(b) The location and size of the nidus

(c) Venous drainage of the AVM

(d) Associated vascular abnormalities

(e) Abnormalities of the adjacent brain parenchyma

(f) The presence of acute or chronic haemorrhage.

PATHOPHYSIOLOGICAL FEATURES OPF AVM

Perinidal Vessels and Flow Regulation in AVMs

The abnormal vessel groups surrounding the nidus Angiographers call "reverse nidus" subsequently may become part of the main nidus[15]. This network of vessels is connected to the nidus and to the normal vasculature as well[16]. Many authors believe that this capillary network contribute not only to post-operative bleeding but also to nidal recurrence. Modja-Modja vessels is a term used to describe the perinidal hypervascular network, these vessels are very fragile that result from a hemodynamic overload state[17]. Obliterating the AVM shunt increases the intravascular pressure of the feeding arteries, which leads to the rupture of these perinidal vessels resulting in intra-operative and/or post-operative bleeding. It may be important to coagulate these vessels at the base of the resection bed, but it is not recommended in eloquent cortical area.

The normal cerebral vessels due to steal effect from AVM or AVF lose their autoregulatory capability when exposed to chronically reduced perfusion pressure; following endovascular occlusion of AVM the pressure in these vessels raise to normal levels. Since these vessels have lost their autoregulatory capability, these vessels cannot respond appropriately to an increase in arterial pressure leading to haemorrhage and or edema. This phenomenon is called Normal Perfusion Pressure breakthrough (NPPB). Spetzler et al proposed this phenomenon first in 1978[18].

Steal Phenomenon in Cerebral AVMs

Single-photon emission CT scan has demonstrated that there is hypoperfusion in the brain surrounding and distant to AVMs leading to seizures and cognitive impairment. This concept is called vascular steal phenomenon and it may be the source of clinical symptoms in patients who present with neurological deficits[19,20].

Treatment for AVM

AVM represents a rare disease and in a recent milieu of generally accepted policy of non-actively treating SM Grade IV and V. Various modalities for treatment are available from surgery to endovascular and radiosurgery.

Surgery

Each neurosurgeon must evaluate (1) Patient and clinical presentation of each particular patient. (2) VM itself, its accessibility, angio-architecture, feeders, drainage. (3) Own institution which should be able to offer any of the treatment modalities. (4) His/her own ability, experience, skills.

All these factors must be evaluated carefully, objectively and above all honestly. Only then the surgery can be offered.

The steps microsurgical treatment approach include the following: (1) perform a craniotomy adequate enough exposure to the AVM, including its arterial feeders and venous outflow; (2) isolate and divide its arterial feeders; (3) circumferentially dissect the nidus from the adjacent brain parenchyma and surrounding neurovascular structures; (4) disconnect the venous outflow after confirming complete disconnection from arterial feeders; and (5) close the wound. The main advantages of microsurgical resection over other treatment options include its high rate of complete nidus obliteration, its ability to immediately eliminate hemorrhage risk,

and its long-term durability. Its main disadvantages are its invasiveness, length of recovery, and associated neurological risks.

Radiosurgery

Obliteration of the AVM is the primary goal for SRS. With obliteration, prevention of hemorrhage from the AVM nidus is achieved. Most studies show AVM obliteration in 70% to 80% of AVMs, and obliteration is typically achieved within 2 to 3 years after treatment[21,22,23,24].

Delayed effects after radiosurgery include adverse radiation effects. During the latency period after SRS, symptomatic changes attributable to adverse radiation effects occur in ≈10% of patients, but this risk varies by AVM location, target volume, and margin dose (dose to surrounding normal tissue). Corticosteroids and, less frequently, bevacizumab have been used to ameliorate symptomatic adverse radiation effects. Permanent neurological changes from adverse radiation effects are seen in 2% to 3% of patients[25,26].

Embolisation

Embolization can be used in a variety of scenarios for ruptured AVMs. As mentioned above, targeted embolization of nidal or perinidal aneurysms may reduce the risk of rerupture[27]. This can be undertaken as the sole treatment of high-grade lesions or as a means of reducing the risk of rerupture in the interval before definitive surgical resection or SRS. Preoperative embolization may facilitate and lower the risks of surgical resection[28]. Typically, the goal of embolization in this scenario is to target inaccessible portions of the AVM or deep arterial feeders that are difficult to control surgically. Finally, embolization as a means of reducing AVM volume in preparation for SRS can also be considered[29].

N-butyl cyanoacrylate and EVOH are commonly used liquid embolisates for the treatment of AVMs. A prospective randomized trial established the equivalence of

these agents in terms of safety and efficacy (comparing N-butyl cyanoacrylate with polyvinyl alcohol and EVOH with N-butyl cyanoacrylate)[30, 31]. The development of detachable tip microcatheters, which allow prolonged EVOH infusion, has made curative embolization of AVMs feasible in select cases[32, 33, 34]. Detachable coils may also be used to close large arterial feeders or high-flow arteriovenous shunts.255 Liquid embolisates and coils are frequently used in combination to treat AVMs[35,36].

Combined Therapy

The combination of treatment modalities, namely endovascular approach and radiosurgical treatment allows for more targeted possibilities and allows for treatment of AVMs which would have historically been deemed untreatable. However, the decision to use the combination must take into account that their risks are cumulative. Each modality has its own risks and each treatment step must be carefully evaluated. The summary of the risks must not exceed those of the natural course. The danger to overuse, especially preoperative embolization is obvious. It also must be highlighted that after each step, the AVM must be evaluated as a new one.

Treament of unruptured AVM

Only 1 randomized controlled trial exists to inform the management of unruptured AVMs: ARUBA. This study recruited 226 adult patients (≥18 years old) with unruptured AVMs between 2007 and 2013 and randomly allocated them to medical management alone or medical management with interventional therapy (eg, resection, embolization, or SRS alone or in combination). A preplanned interim analysis was reviewed by the trial's independent Data and Safety Monitoring Board on April 15, 2013. The data showed that after a mean follow-up of 33 months, the risk of stroke or death in the intervention group (30.7%) was >3 times higher than in the medical management group (10.1%).

AIMS AND OBJECTIVES

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To assess the pre-operative and post-operative neurological deficit in operated cases of cerebral AVM, located on eloquent area on MRI.

METHODOLOGY

METHODOLOGY

The present study was a prospective study, including all the patients who will be undergoing surgery for cerebral AVM located on eloquent areas on MRI in the department of neurosurgery, SCTIMST. Total number of cases to be included in the study are 13. All patients underwent Cerebral Angiography to asses size of AVM, Arterial supply and to know venous drainage. These investigations are as per standard protocol for evaluation of AVM. Patient will undergo thorough Neurological examination to assess for any deficits pertaining to location of AVM. After surgery patient will be reassessed clinically for any neurological deficits secondary to excision of AVM.

ELIGIBILITY

Inclusion criteria: All cases of AVM located in eloquent area irrespective of grade, operated in SCTIMST under department of Neurosurgery will be included in study.
Patient undergoing pre-operative embolization will be included in the sudy

Exclusion criteria:

AVMs located in non-eloquent areas.

Bled AVM will be excluded from the study

Data collection:

The data regarding demographic profile, clinical presentation, pre and postoperative neurological examination, details of surgical/radiation treatment, pre and postoperative neurological deficit, postoperative surgical and medical complications were assessed. The radiologic data was recorded. The patient's status will be assessed preoperatively, on POD-1, POD-3 and at follow up at 3 months.

Defining outcome: Post-operative neurological deficit on follow up at 3 months will be was as simplified outcome measure.

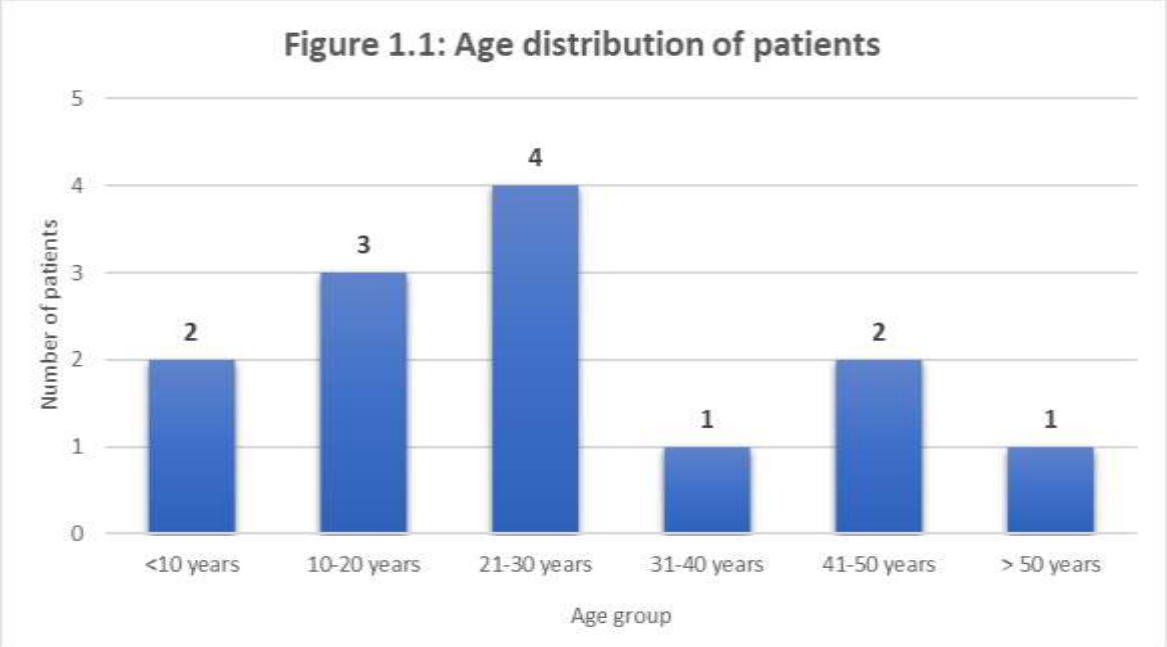
RESULTS

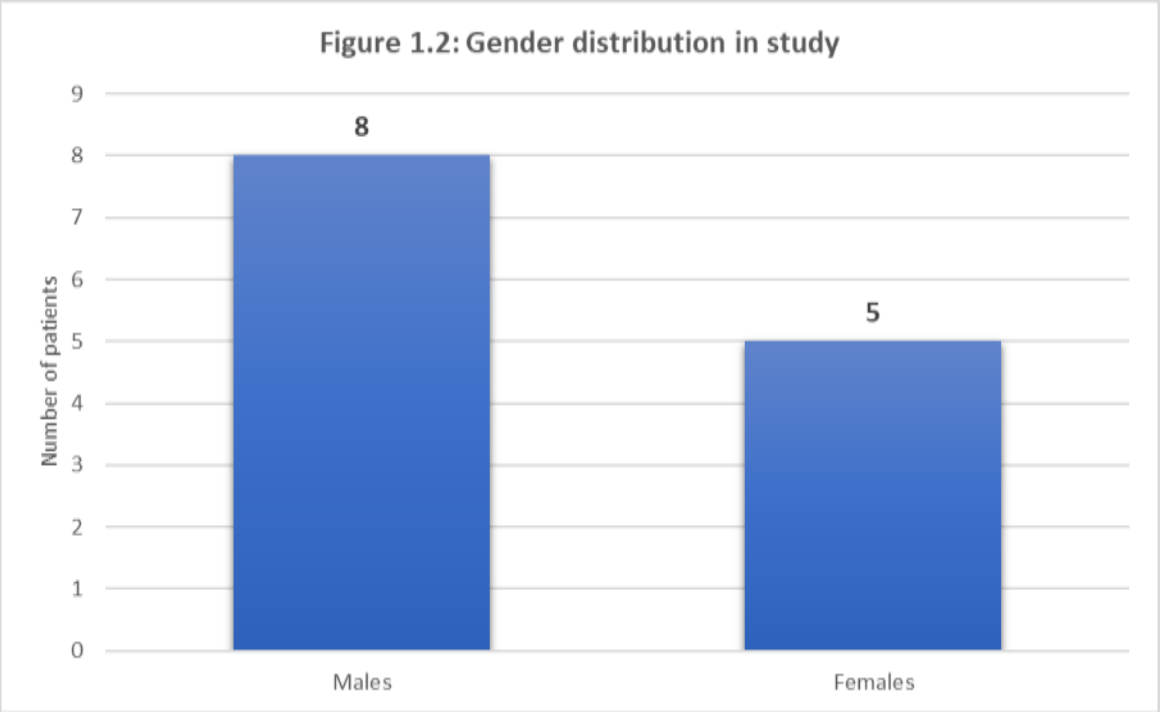
RESULTS

1. Demographic details

The mean age was found to be 25.92 ± 13.99 for the enrolled patients. Majority of the enrolled patients were noted to be males (n=8/13). Most of the enrolled patients were found to be between age 21-30 years while three patients were found to be in the age group pf 10-20 years. (Table 4.1, figure 1.1, figure 1.2).

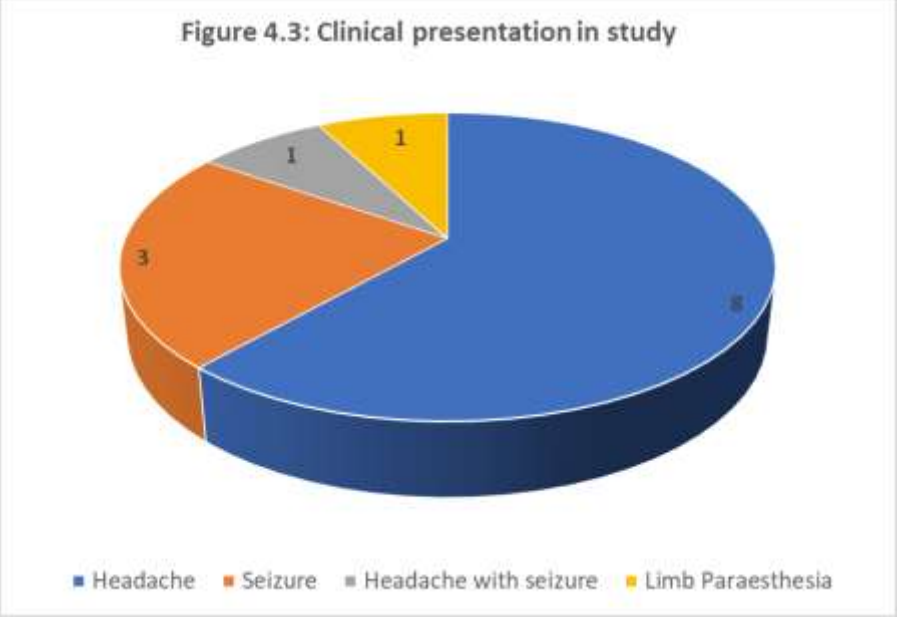
Table 4.1: Demographic details of enrolled patients in study	
Parameter Assessed	*Calculated value*
Mean age (years)	25.92 ± 13.99
Median age (years)	23
Minimum age (years)	6
Maximum age (years)	51
Number of males	8
Number of females	5





2. Clinical presentation in study

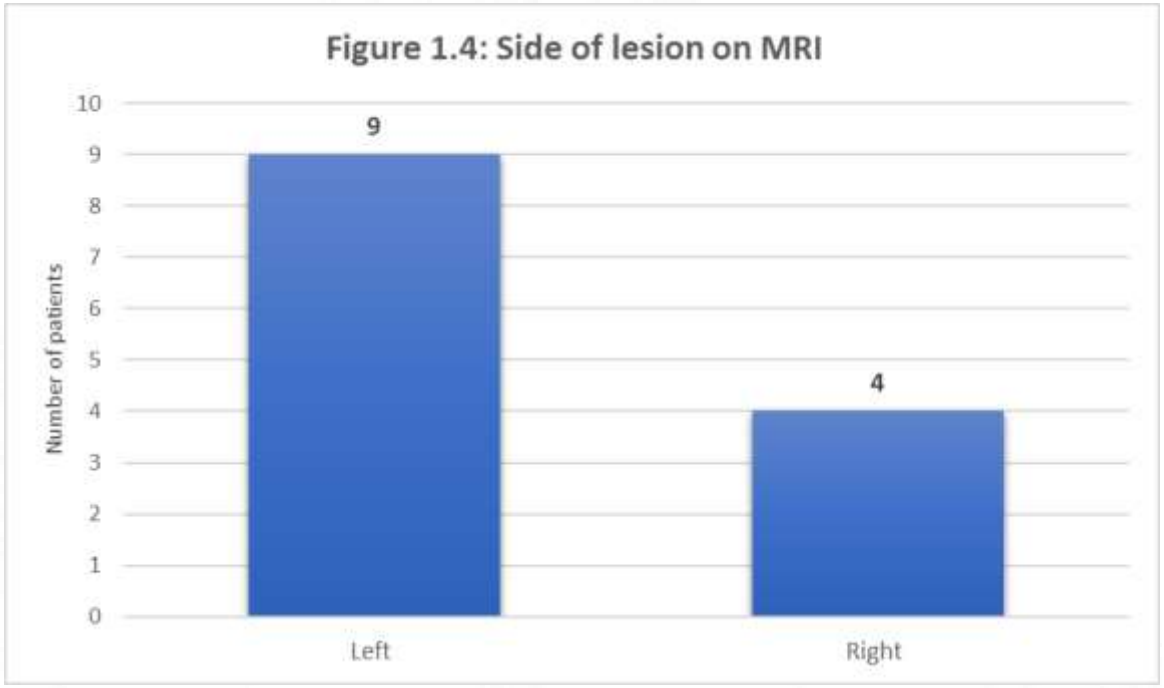
The most common clinical feature noted in the study was headache alone, noted in 8 patients. This was followed by seizure in 3 patients, headache with seizure in one patient and limb paresthesia in one patient (figure 1.3).



3. Side of lesion on MRI

On MRI assessment, 9 patients had left sided lesion while 4 patients had right sided lesion. (Figure 1.4)

The nidus of AVM on assessment was found to be compact in 4 patients and diffuse in 9 patients.



4. Location of AVM on MRI

The commonest locations for AVM on MRI were insular AVM and occipital, both seen in two patients each. Other locations for AVM noted were angular, cerebellum, frontal opercular, parietal, post-central gyrus, pre-frontal and motor cortex, parieto-occipital, pre-rolandic, and superior parietal (Table 4.2).

Table 4.2: Location of AVM on MRI assessment

Location of AVM on MRI	**Number of patients**
Insular AVM	2
Occipital	2
Angular AVM	1
Cerebellar hemisphere	1
Frontal opercular AVM	1
Parietal supramarginal	1
Post central Gyrus	1
Pre-frontal and motor cortex	2
Parieto-occipital	1
Superior parietal	1

5. Arterial feeders in study

The most common arterial feeders noted in study were MCA (angular and parietal branches) and PCA (occipital branch) together in 2 patients, MCA (cortical branches) in 2 patients, and PCA (cortical branches) in 2 patients (Table 4.3).

Table 4.3: Arterial feeders noted in study

Arterial Feeders	**Number of patients**
MCA (angular and parietal branches) and PCA (occipital branch)	2
MCA (cortical branches)	2
PCA (cortical branches)	2
AICA, PICA, SCA (cortical branches)	1
MCA (angular and parietal branches)	1
MCA (Cortical and collosomarginal branches)	1
MCA (hypertrophied branch)	1
MCA (parietal branch)	1
MCA (superior and parietal branches)	1
MCA (superior division)	1

6. Venous drainage in study

The commonest venous drainage noted in the study was superficial saggital sinus noted in 11 patients, while 2 patients showed deep drainage in transverse sinus and inferior vermian vein. (Table 4.4)

Table 4.4: Venous drainage noted in study	
Venous drainage	**Number of patients**
Cortical vein into SSS	11
Transverse sinus	1
Superficial drainage through dilated inferior vermian vein	1
Deep Venous Drainage	2

7. Neurological grading of patients:

Majority of patients in the study (n=6) belonged to neurological grade 3. 4 patients in study had neurological grade 2 while 3 patients belonged to neurological grade 4 (Figure 1.5).

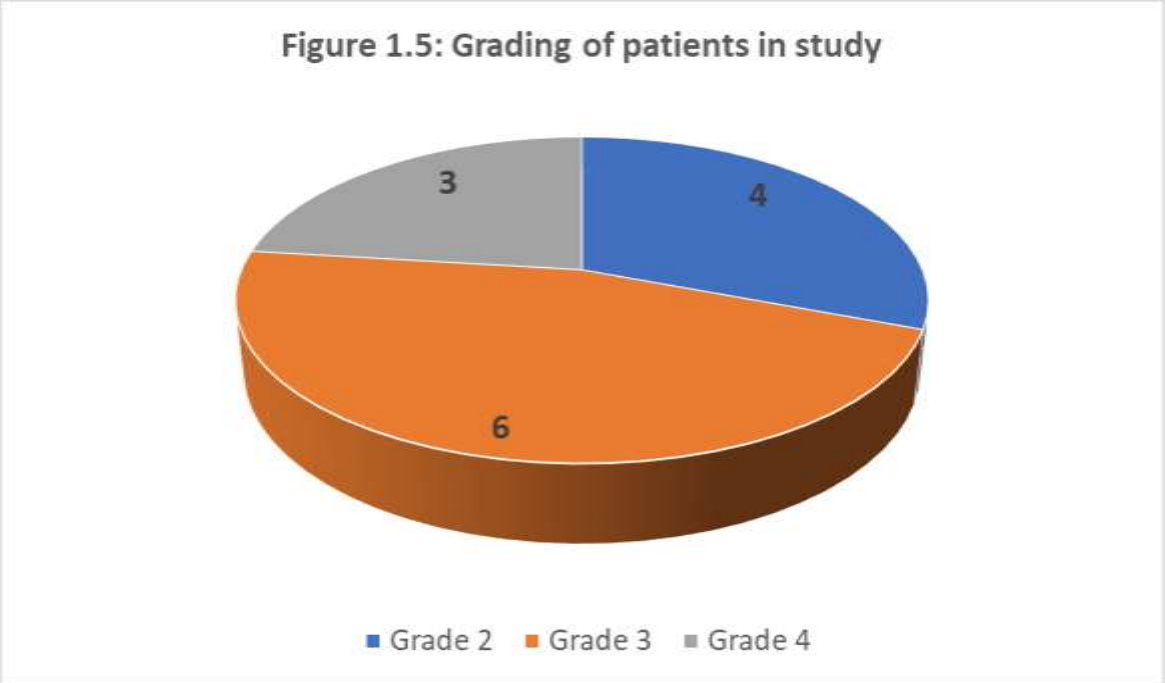


Table 4.5 below gives a summary of the key demographic and AVM characteristics in study.

Table 4.5: Demographic and AVM characteristics of 13 enrolled patients in study	
Parameter Assessed	*Calculated value / Number of patients*
Mean age (years)	25.92 ± 13.99
Number of males	8
Number of females	5
M:F ratio	1.6:1
Side (L/R) ratio	9/4
Diffuseness (Diffuse/Compact)	9/4
Venous drainage (superficial / deep)	11/2
Neurological grading (Grade 2/3/4)	4/6/3

8. Post-operative deficit noted in study

In the study, on day 1, 6 patients had no deficit while 7 had post-operative deficit. The post-operative deficits noted in study in one patient each included dysphasia, seizure, right homonymous hemianopia. Left hand grip weakness, aphasia with left sided limb weakness and right UMN palsy, and gaze evoked nystagmus (Table 4.6).

Table 4.6: Postoperative neurological deficit post-surgery on day 1	
Deficit status on Day 1	*Number of patients*
No deficit	6
Deficit or post-operative abnormality	7
Deficit or post-operative abnormality	
Dysphasia	1
Seizure	3
Right homonymous hemianopia	1
Left hand grip and wrist weakness	1
Aphasia, left sided limb weakness, right UMN palsy	1
Immediate post-operative seizure requiring sedation and ventilation	1
Gaze evoked nystagmus	1

On day 3 of follow-up, 2 of the 7 patients with deficits on day 1 improved, while 5 of the patients had new or persistent deficits. On 3rd month follow-up 6 of the 7 patients with deficits on day 1 improved, while 1 of the patients had new or persistent deficits. (Table 4.7)

Table 4.7: Follow-up deficit status on day 3 and month 3		
Deficit on day 1	**Status on day 3**	**Status at month 3**
Dysphasia	Persistent	Improved
Seizure	Right hemifield defect	Improved
Right homonymous hemianopia	Improved	Improved
Left hand grip and wrist weakness	Improved	Improved
Aphasia, left sided limb weakness, right UMN palsy	Persistent	Improved
Immediate post-operative seizure requiring sedation and ventilation	Focal seizure, intermittent comprehension, poor calculation, walk with ataxia	Improved
Gaze evoked nystagmus	Swaying to left	Improved
Total	**New/ persistent deficit = 5** **Improved = 2**	**New or persistent deficit = nil** **Improved = 7**

9. Pre-operative and post-operative IQ and executive function comparison

On comparing the pre-operative and post-operative IQ as well as executive function percentile, no significant difference was found statistically (p>0.05) (Table 4.8)

Table 4.8: Pre-operative and post-operative IQ and executive function comparison			
Parameter assessed	*Pre-operative*	*Post-operative*	*P value*
Mean executive percentile	72 ± 19.74	67 ± 24.74	0.58
Mean IQ	84.08 ± 17.16	83.1 ± 13.05	0.72

P value >0.05 considered not significant by paired t test

On comparing the pre-operative and post-operative IQ as well as executive function percentile in sub-groups of both right and left sided AVM, no significant difference was found statistically (p>0.05). However, on intergroup analysis, right sided sub-group had significantly higher pre-operative as well as post-operative values than left sided sub-group (p<0.05). (Table 4.9)

Table 4.9: Pre-operative and post-operative IQ based on side of AVM			
Side of AVM	*Pre-operative*	*Post-operative*	*P value (intragroup)*
Right sided (n=4)	103.75 ± 6.29	97 ± 9.23	0.34
Left sided (n=9)	74.25 ± 10.55	76.85 ± 10.2	0.62
P value (intergroup)	**<0.01**	**<0.01**	

P value >0.05 considered not significant by paired t test (intragroup analysis)

P value < 0.05 considered significant by unpaired t test (intergroup analysis)

10. Early deficit (day 1 and day 3) based on side of AVM:

On comparing the early deficit in right and left subgroups (based on AVM side), 2 of the 4 patients in right sided AVM subgroup had deficit on day 1 while 1 of 4 had deficit on day 3. In left sided AVM sub-group, 5 of 9 patients had deficit on day 1, while 4 of 9 patients had deficit on day 3 follow-up (Table 4.10)

Table 4.10: Early deficit (day 1 and day 3) based on side of AVM

Side of lesion	**Deficit on day 1**	**Status on day 3**
Right (n=4)	No deficit (n=2)	No deficit (n=2)
	Seizure	Right hemifield defect
	Left hand grip and wrist weakness	Improved
Left (n=9)	No deficit (n=4)	No deficit (n=4)
	Dysphasia	Persistent
	Right homonymous hemianopia	Improved
	Aphasia, left sided limb weakness, right UMN palsy	Persistent
	Immediate post-operative seizure requiring sedation and ventilation	Focal seizure, intermittent comprehension, poor calculation, walk with ataxia
	Gaze evoked nystagmus	Swaying to left

11. Early deficit based on grade of AVM

On comparing the early deficit in based on grade of AVM, 1 of the 4 patients in grade 2 AVM subgroup had deficit on day 1 while none had deficit on day 3. In grade 3 AVM sub-group, 4 of 6 patients had deficit on day 1, while 3 of 6 patients had deficit on day 3 follow-up. In the grade 4 AVM sub-group, 2 of 3 patients had deficit on both day 1 and day 3. (Table 4.11)

Table 4.11: Early deficit (day 1 and day 3) based on grade of AVM

AVM Grade	**Deficit on day 1**	**Status on day 3**
Grade 2 (n=4)	No deficit (n=3)	No deficit (n=3)
	Right homonymous hemianopia	Improved
Grade 3 (n=6)	No deficit (n=2)	No deficit (n=2)
	Dysphasia	Persistent
	Left hand grip and wrist weakness	Improved
	Immediate post-operative seizure requiring sedation and ventilation	Focal seizure, intermittent comprehension, poor calculation, walk with ataxia
	Gaze evoked nystagmus	Swaying to left
Grade 4 (n=3)	No deficit (n=1)	No deficit (n=1)
	Aphasia, left sided limb weakness, right UMN palsy	Persistent
	Seizure	Right hemifield defect

12. Early deficit (day 1 and day 3) based on venous drainage

On comparing the early deficit in based on venous drainage, 6 of the 11 patients in superficial venous drainage subgroup had deficit on day 1 while 4 of 11 had deficit on day 3. In deep venous drainage sub-group, 1 of 2 patients had deficit both on day 1 and day 3 follow-up (Table 4.12)

Table 5.12: Early deficit (day 1 and day 3) based on venous drainage

Venous drainage	**Deficit on day 1**	**Status on day 3**
Superficial (n=11)	No deficit (n=5)	No deficit (n=5)
	Seizure	Right hemifield defect
	Left hand grip and wrist weakness	Improved
	Dysphasia	Persistent
	Right homonymous hemianopia	Improved
	Aphasia, left sided limb weakness, right UMN palsy	Persistent
	Immediate post-operative seizure requiring sedation and ventilation	Focal seizure, intermittent comprehension, poor calculation, walk with ataxia
Deep (n=2)	No deficit (n=1)	No deficit (n=1)
	Gaze evoked nystagmus	Swaying to left

13. Early deficit (day 1 and day 3) based on AVM nidus

On comparing the early deficit between compact and diffuse AVM nidus, 1 of the 4 patients in compact AVM subgroup had deficit on day 1 while none had deficit on day 3. In diffuse AVM sub-group, 6 of 9 patients had deficit on day 1, while 5 of 9 patients had deficit on day 3 follow-up (Table 5.13)

Table 4.13: Early deficit (day 1 and day 3) based on AVM nidus

AVM nidus	**Deficit on day 1**	**Status on day 3**
Compact (n=4)	No deficit (n=3)	No deficit (n=3)
	Right homonymous hemianopia	Improved
Diffuse (n=9)	No deficit (n=3)	No deficit (n=3)
	Dysphasia	Persistent
	Left hand grip and wrist weakness	Improved
	Immediate post-operative seizure requiring sedation and ventilation	Focal seizure, intermittent comprehension, poor calculation, walk with ataxia
	Gaze evoked nystagmus	Swaying to left
	Aphasia, left sided limb weakness, right UMN palsy	Persistent
	Seizure	Right hemifield defect

14- Seizure Outcome-

Of the 3 patients who presented with seizure all 3 were were seizure free at three months of follow up (Engel Class I-A), Two patients had developed seizure post-operatively. One patient achieved Engel class I-A and other Engel Class II.

DISCUSSION

DISCUSSION

AVMs are considered congenital lesions that are likely present prior to the maturation of eloquent areas, suggesting that patients have an increased susceptibility to functional displacement given the inherent plasticity of the cortex during growth and development. Although they may be located in close proximity to eloquent areas, unruptured AVM usually do not present with functional deficits. Instead, the most common presenting symptoms are seizures or headaches, and many patients remain symptomatic. Chronic hypoperfusion due to vascular steal from cerebral AVM can result in a translocation of eloquent neurological functions to other brain areas, a phenomenon known as cortical plasticity. Cortical plasticity has been more extensively studied in patients with intrinsic brain tumors and ischemic stroke. Due to the scarcity of AVM relative to the aforementioned diseases, the analyses of cortical plasticity in AVM patients is more challenging to undertake.

Motor Area AVM

Lin et al, retrospectively assessed 48 patients for risk factors for worsened muscle strength after the surgical treatment of AVMs located on eloquent motor area. Functional MRI and DTI Tractography were done preoperatively. Lesion to corticospinal tract distance (LCD) on DTI and lesion to activation area distance and cortical reorganization on fMRI. They concluded that an AVM with a nidus in contact with tracked eloquent fibers and having a large size is more likely to be associated with worsened muscle strength after surgery in patients with eloquent motor area AVMs[37]. Lin et al, conducted another retrospective study to determine the relationship between preoperative functional findings and surgical outcomes in patients with motor cortical AVM. Eighteen patients were enrolled, fMRI and DTI was done to assess cortical and corticospinal tract reorganisation. They concluded that Diffuse nidus AVM, large size of the AVM and involvement of corticospinal tract were associated poor motor outcome rather than cortical reorganisation[38].

Lee et al. conducted a retrospective analysis of 22 patients with AVMs. Patients were divided into three groups according to the location of the lesion. They divide patients into 3 groups. Group 1, the control group, patients whose AVM were greater than two gyri or sulci away from motor cortex. Group 2, defined as being between 1 and 2 sulci or gyri away (adjacent to motor area) and group 3, which constitutes an AVM directly overlying the motor areas. A motor finger-tapping paradigm for the upper limb and/or knee-flexion paradigm for the lower limb was implemented during fMRI sequence acquisition. Cortical reorganization was only observed in group 3 patients, and it was statistically significant when compared with group 1 patients. In group 3 patients, excision took place in three (50%) patients. Mean follow-up for those patients having undergone excision was 44 months, with no new or worsening of previous neurological deficits being noted after intervention[39].

Yuming Jiao et al assessed 125 patients retrospectively. They classified their AVMs into 4 motor area related groups. (I) nidus involving PMA and/or SMAs; (II) nidus involving the precentral gyrus; (III) nidus involving the CST and superior to the posterior limb of the internal capsule; (IV) nidus that invaded the CST at or inferior to the level of posterior limb of the internal capsule. They divided type IV into type IVa (nidus without AChA feeding) and type IVb (nidus with AChA feeding). They assessed variables like the nidus size, eloquence, SM grade, and presence of deep venous drainage and deep perforating arterial. They observed that motor area subtype, diffuse nidus, arterial supply from deep perforating feeders and deep venous drainage had statistically significant poor motor power outcome on long term outcome.

Alkadhi et al., In a prospective study by used fMRI to map the cortical organization in nine right-handed patients with brain AVMs directly involving the hand or foot region of the primary motor cortex. Cortical motor hand and foot representations were mapped in nine right-handed patients harboring AVMs occupying the hand (n = 6) or foot (n = 3) region of the primary motor cortex. None of the patients exhibited motor deficits. In eight patients, both right and left extremities were tested;

in one patient, only the hand contralateral to the AVM was examined. They compared activation of localisation in affected hemisphere to the contralateral hemisphere. Cortical activation showed three patterns[40]:

1) functional displacement within the affected primary motor cortex independent of the structural distortion induced by the AVM,

2) presence of activation within the unaffected primary motor cortex ipsilateral to the moving extremity without activation in the affected primary motor cortex, and

3) prominent activation in nonprimary motor areas without activation in either the affected or unaffected primary motor cortex[40].

In our study, we had two patient who had AVM on precental gryus. Both patients had weakness in limbs post-operatively. On follow up at 3months both patients had recovered completely. Patients with AVM located 1 or more gyri away from motor area did not develop any motor weakness post-operatively.

Occipital Lobe AVM.

M.J. Kupersmith, et al, conducted a retrospective study to assess the outcome of 70 patients with occipital AVM. Homonymous hemianopia and headache were the most common symptom. In their visual filed defects (VFDs) were more common with AVMs located on medial surface compared to lateral surface. VFDs were more common and more severe with bled AVMs which was statistically significant. Twenty patients underwent surgery for elimination of AVM. Overall visual fields were worse in 15 patients, unchanged in 22, and improved in eight. They concluded that visual field outcomes did not differ irrespective of treatment modality (Embolisation vs Radiotherapy vs Surgery)[41].

Xianzeng Tong et al, assessed 42 consecutive patients retrospectively. The assesed patient parameters (age, sex, and history of haemorrhage) and AVM characteristics (size, side, venous drainage, Spetzler-Martin grade, and diffuseness). VFDs were identified in 14 patients, among which 12 patients presented had with hemorrhage and 2 presented with nonhemorrhagic chronic headache. VFDs were more common in patients with ruptured AVMs and was statistically significant. Unlike other lesions involving the optic radiation and visual cortex, the frequency of VFDs in occipital AVMs did not correlate with the AVM to Optic Radiation (AVM-OR) and AVM to Visual cortex (AVM-VC) distances. In this series, 22 patients presented with a zero distance of the AVM-OR or AVM-VC or both. Of these, 6 patients had a history of hemorrhage and presented with preexisting VFDs. The other 16 patients with unruptured AVMs had normal VFs[42].

Amir R. Dehdashti assessed 135 patients retrospectively treated at their institute. They assessed multidisciplinary treatment for occipital AVM. Headache was most common symptom. Thirty-three patients had visual deficit at the time of presentation (11 bled and 22 unbled). In the surgical group, 15 patients had preoperative VF defects. Five showed improvement, 8 showed no change, and 2 had worsening of their partial defect to a complete homonymous hemianopia. There were 6 (13%) new VF deficits (4 hemianopia and 2 quadrantanopia); only 1 case of hemianopia improved to quadrantanopia at later follow-up. Therefore, the total rate of worsened preoperative visual deficit (2 of 46) or a new visual deficit after surgery (6 of 46) was 17%[43].

In our study, we had two patients with lesion in the occipital lobe with no deficits pre-opertively. One patient had visual field defect immediate post-operatively which improved completely at follow up at 3 months.

Neuropsychological Outcome

Andersen et al, in gthe year 1988 studied mental and physical outcome in 25 conservatively treated AVM patients followed-up for a mean of 10.6 years. The main factors influencing neuropsychological outcome in patients with AVMs were:

1. Haemorrhagic presentation with possible focal neurological and cognitive domain deficit according to lesion location
2. Frequency of seizures and severity of epilepsy
3. Steal phenomenon
4. Type and duration of symptoms and initial level of consciousness. The authors showed that only 25% of their patients will be socially disabled in the long term[44].

Mahalick et al., compared neuropsychological performance in 24 AVM patients with 24 matched (normal) controls. Patients harbouring AVMs exhibited varying degrees of impairment in verbal and visuospatial processing depending on the location of the lesion in the dominant or non-dominant hemisphere. 14 patients before and after microsurgical excision were assessed. Improvement in neurocognitive functions was observed in hemispheres ipsilateral to AVMs and to a lesser extent in contralateral hemispheres, again suggesting the role of the cerebrovascular steal phenomenon in AVM patients[45].

Marshall et al. prospectively studied the neuropsychological and psychosocial outcome in 64 patients undergoing resection of brain AVMs. The neuropsychological evaluation was performed prior to surgery, at 1 month and 1 year postoperatively. The observed decreased neuropsychological function at 1month post-surgery, but all neuropsychological tests showed a mild improvement 1 year after surgery compared with pre-operative values. The difference between 1 year and early post-operative values was pronounced. Final outcome did not differ significantly for patients presenting with haemorrhage[46].

In our study, Neuropsychology was assessed pre-operatively and at 3 months post operatively. Improvement was seen in IQ patients with AVM located on left side and mild deterioration in those operated on the left side. There was mild deterioration seen in executive function of the patients irrespective of the location of the AVM.

Limitations :

1. Small sample size (n=13).
2. Bled aneurysms were not included in this study to compare outcome between bled and unbled aneurysms.

CONCLUSION

CONCLUSION

Patients with AVM on eloquent area can be operated safely in experinced without any long term defecits. Improvement was noted in IQ with patients wit AVM located on the left.

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DUPLICATE

Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-16)

SCT/IEC/1569 /OCTOBER-2020

28.12.2020

Dr. Harshavardhan Biradar
Senior Resident
Department of Neurosurgery
SCTIMST, Thiruvananthapuram

Dear Dr. Harshavardhan Biradar,
Thank you for submitting documents related to your proposal titled "**ASSESSMENT OF NEURONAL PLASTICITY IN ARTERIOVENOUS MALFORMATIONS(AVM) WITH OVERLAP OF ELOQUENT AREAS CORRELATION BETWEEN LOCATION ON MRI AND PRE AND POST OPERATIVE NEUROLOGICAL DEFICIT** (IEC/1569)" to the IEC for review.

The following documents were reviewed

1. Check list
2. Covering letter addressed to Chairman dated 17.08.2020
3. Covering Letter from HOD, Dr.Easwer to Chairman IEC dated 17.08.2020
4. TAC Approval with Comments and responses dated 11/05/2020
5. TAC Application form
6. IEC Application signed and dated 17/08/2020
7. Consent form(English)
8. Consent form(Malayalam)
9. CV of Co-PI Dr.Mathew Abraham with TNMC number (without signature)dt.13.10.2019
10. Signed CV of PI with TNMC Number dated 09.10.2019
11. Patient Information Sheet (English)
12. Patient Information Sheet (Malayalam)
13. Proforma

The following members of the Students Sub-Committee of the Institutional Ethics Committee participated in the discussions held between August 21 – October 27 2020 at the offices and residences of the members

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. R V G Menon	M Tech, PhD	Male	Lay Person (Chairman)	No
2.	Dr. Harikrishnan S	MD, DM (Cardiology) DNB (Cardiology)	Male	Clinician	Yes
3.	Dr. Kala Kesavan. P	MBBS, MD	Female	Basic Medical Scientist	No
4.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
5.	Dr. Rema M. N	MD	Female	Basic Medical Scientist	No
6.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
7.	Dr. Mala Ramanathan	PhD	Female	Social Scientist (Member Secretary)	Yes

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,

Mala Ramanathan
Member Secretary, IEC

Proforma

Title: Assessment of neuronal plasticity in Arteriovenous Malformations (AVM) with overlap on eloquent areas correlation between location on MRI and pre and postoperative neurological deficit.

Sl no

Age/sex

Education

Occupation

Diagnosis

DOA

DOS

DOD

Chief complaint

History of present illness

Past history

Treatment history

General examination

Systemic examination

<u>Neurological Examination</u>

Higher Functions

MMSE

Frontal assessment battery

Neuropsychological assessment

Cranial nerve assessment Right Left

Olfactory

Optic

	Right	Left
VA: Near Vision Far vision		
Visual field		

Fundus

VEP

CN III, IV & VI

Ocular movements

Pupils

Pupillary Reactions

Trigeminal nerve

Sensory

Motor

Corneal Reflex

Facial nerve

Vestibulocochlear nerve

CN IX &X

- Uvula
- Phonation
- Palatal Movements
- Gag Reflex

CN XI

CN XII

MOTOR EXAMINATION

- Bulk
- Tone
- Power

INVOLUNTARY MOVEMENTS

REFLEXES

- Deep Tendon Reflexes
- Superficial reflexes

Cerebellar signs

Sensory systems

Gait and stance

Skull and spine

Investigations

CT

- Size
- Location
- Bleed
- Others

MRI

- Size
- Location
- Arterial Supply
- Venous drainage
- Other

CT Angio

- Size
- Arterial supply
- Venous Drainage

DSA

- Size
- Arterial supply
- Venous Drainage
- Anuerysm

OTHER INVESTIGATIONS

SURGERY

Approach

Intraoperative finding

HPR

Post-Op CT Scan

Postoperative

Neurological status

Immediate

POD-1

POD 3

Post-Operative Complications

Follow up

Sl no	POD	Neurological Status	DSA
1			
2			
3			

CONSENT FORM

TITLE OF THE STUDY: **Assessment of neuronal plasticity in Arteriovenous Malformations (AVM) with overlap on eloquent areas correlation between location on MRI and pre and postoperative neurological deficit**

Study number:

Participant's name: _____

Date of Birth / Age (in years): _____

Son/daughter of _____

(Please tick boxes) •

I declare that I have read the above information provided to me regarding the study – "**Assessment of neuronal plasticity in Arteriovenous Malformations (AVM) with overlap on eloquent areas correlation between location on MRI and pre and postoperative neurological deficit .**"- and have clarified any doubts that I had. [ ]

I understand that my participation in this study is entirely voluntary and that i am free to withdraw the permission to continue my participation at any time without affecting my usual treatment or my legal rights. [ ]

I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if i withdraw from the trial. I agree to this access. [ ]

I understand that my identity will not be revealed in any information released to third parties or published [ ]

I voluntarily agree to take part in this study [ ]

I have received a copy of this signed consent form [ ]

During this study patient of patient relatives will not bare any expenditure for the study.

Name: _____

Signature:_____

Date:_____

Name of witness:_____

Relation to participant:_____

Date: _____

(Person Obtaining Consent) I, _____ attest that the requirements for informed consent for the medical research project described in this form have been satisfied. I have discussed the research project with the participant and explained to him or her in nontechnical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that i encouraged the participant to ask questions and that all questions asked were answered.

_____ _____

Name and Signature of Person Obtaining Consent

സമ്മതപത്രം

പഠനശീർഷകം: ആർട്ടീരിയോ വീനസ് രൂപവൈകൃതത്തിലെ (എവിഎം) ന്യൂറോണലുകളുടെ വഴങ്ങുന്ന സ്വഭാവത്തന്റെ സ്പഷ്ടമായി സൂചിപ്പിക്കുന്ന മേഖലകളിലെ വ്യപനവും എംആർഐയിലെ സ്ഥാനവും തമ്മിലുള്ള പാരസ്പര്യവും ശസ്ത്രക്രിയയ്ക്ക് മുമ്പും ശേഷവുമുള്ള പോരായ്മകളുടെ. വിലയിരുത്തലും.

പഠന നമ്പർ:

പങ്കെടുക്കുന്നയാളുടെ ആശുപത്രി നമ്പർ: _____

ജനനതീയതി/വയസ്സ് (വർഷത്തിൽ): _____

_____ മകൻ/മകൾ

(ദയവായി കോളങ്ങളിൽ ശരി അടയാളപ്പെടുത്തുക)

ആർട്ടീരിയോ വീനസ് രൂപവൈകൃതത്തിലെ (എവിഎം) ന്യൂറോണലുകളുടെ വഴങ്ങുന്ന സ്വഭാവത്തന്റെ സ്പഷ്ടമായി സൂചിപ്പിക്കുന്ന മേഖലകളിലെ വ്യപനവും എംആർഐയിലെ സ്ഥാനവും തമ്മിലുള്ള പാരസ്പര്യവും ശസ്ത്രക്രിയയ്ക്ക് മുമ്പും ശേഷവുമുള്ള പോരായ്മകളുടെ. വിലയിരുത്തലും.എന്ന പഠന സംബന്ധമായി മുകളിൽ നൽകിയ വിവരങ്ങൾവായിച്ചതായും എന്റെ സംശയങ്ങൾ പരിഹരിച്ചതായും ഞാൻ പ്രഖ്യാപിക്കുന്നു. [ ]

ഈ പഠനത്തിലെ എന്റെ പങ്കാളിത്തം സ്വമേധയായാണെന്നും പതിവ് ചികിത്സയെയോ നിയമപരമായ അവകാശങ്ങളെയോ ബാധിക്കാതെ ഏതു സമയത്തും എന്റെ അനുവാദം പിൻവലിക്കാമെന്നും ഞാൻ മനസ്സിലാക്കുന്നു. [ ]

ഞാൻ അനുവാദം പിൻവലിച്ചാലും എന്റെ ആരോഗ്യ രേഖകൾ പഠന സംഘാംഗങ്ങൾക്കും ഇൻസ്റ്റിറ്റ്യൂഷണൽ എത്തിക്സ് കമ്മറ്റി അംഗങ്ങൾക്കും പരിശോധിക്കാൻ എന്റെ അനുവാദം ആവശ്യമില്ലെന്നും ഞാൻ മനസ്സിലാക്കുന്നു. അതിന് ഞാൻ സമ്മതിക്കുന്നു [ ]

മൂന്നാം കക്ഷികൾക്ക് നൽകുമ്പോഴോ പ്രസിദ്ധീകരിക്കുമ്പോഴോ എന്നെ തിരിച്ചറിയാനുതകുന്ന വിവരങ്ങൾ നൽകില്ലെന്ന് ഞാൻ മനസ്സിലാക്കുന്നു. [ ]

ഈ പഠനത്തിൽ സ്വമേധയാ പങ്കെടുക്കൻ ഞാൻ സമ്മതിക്കുന്നു. [ ]

ഈ സമ്മതപത്രത്തിന്റെ ഒപ്പിട്ട ഒരു പ്രതി എനിക്ക് ലഭിച്ചു. [ ]

പേര്: _____

ഒപ്പ്:_____

തീയതി:_____

സാക്ഷിയുടെ പേര്:_____

പങ്കെടുക്കുന്നയാളുമായുള്ള ബന്ധം:_____

തീയതി: _____

സമ്മതപത്രം വാങ്ങുന്ന ആൾ

മെഡിക്കൽ റിസർച്ച് പ്രോജക്ടിനാവശ്യമായ സമ്മതപത്രത്തിനു വേണ്ടുന്ന എല്ലാ ഘടകങ്ങളും തൃപ്തികരമായി നിർവഹിച്ചിരിക്കുന്നുവെന്ന് ഞാൻ ബോധ്യപ്പെടുത്തുന്നു. പഠനപങ്കാളിയുമായി ഗവേഷണ പദ്ധതിയെപ്പറ്റി സാങ്കേതികേതര പദങ്ങളുപയോഗിച്ച് എല്ലാ വിവരങ്ങളെപ്പറ്റിയും ചർച്ച നടത്തുകയും പ്രതീക്ഷിക്കാവുന്ന അപകടസാധ്യതകളും പാർശ്വഫലങ്ങളും വിശദീകരിക്കുകയും ചെയ്തു. പങ്കാളിയെ ചോദ്യങ്ങൾ ചോദിക്കാൻ പ്രേരിപ്പിക്കുകയും എല്ലാ ചോദ്യങ്ങൾക്കും ഉത്തരം നൽകുകയും ചെയ്തു എന്നും ഞാൻ സാക്ഷ്യപ്പെടുത്തുന്നു.

സമ്മതപത്രംവാങ്ങുന്ന ആളുടെ പേര്

ഒപ്പ് തീയതി