SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY

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ENDOVASCULAR TREATMENT OF BRAIN ARTERIO-VENOUS MALFORMATIONS WITH ONYX

PROJECT REPORT FOR

DM NEURORADIOLOGY

SEPTEMBER, 2009

DEPARTMENT OF IMAGING SCIENCES AND INTERVENTIONAL RADIOLOGY

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CERTIFICATE

This is to certify that the work contained in this thesis have been carried out by ***Dr. Milan B. Jolapara*** *in the Department of Imaging Sciences and Interventional Radiology, Sree Chitra Tirunal Institute of Medical Sciences and Technology, Trivandrum, during his rotatory postings as per schedule, under my guidance and is to my satisfaction.*

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DECLARATION

*I, **Dr. Milan B. Jolapara** hereby declare that I have actually carried out the project "**Endovascular Treatment of Brain Arterio-Venous Malformations with Onyx**" independently under supervision and guidance in this institute.*

Date : Sep 2009.
Trivandrum.

Dr. Milan B. Jolapara

ACKNOWLEDGEMENTS

It is my proud privilege to have had the opportunity to work under the exemplary guidance of my Professor and Head of the Department of Imaging Sciences & Interventional Radiology, Dr. A.K. Gupta. With an absolutely positive attitude towards matters in life, his constant encouragement and support have always been invaluable for me. It is beyond words for me to express my gratitude towards him.

I express my deep, sincere gratitude to all my teachers in radiology – past and present – it has been their vision and blessings that I had the opportunity to work at this institute.

I thank honorable ex-Director of the institute, Dr. K.Mohandas for permitting me to carry out this study.

I sincerely thank Dr. T.R Kapilamoorthy, Additional Professor of Radiology; Dr. C. Kesavadas, Additional Professor of Radiology; Dr. Jayashree, Scientist, Department of Radiology; Dr. Bejoy Thomas, Associate Professor of Radiology; Dr. Narendra Bodhey, Associate Professor of Radiology; Dr.Hima Pendharkar & Dr. Wangju Sumyan, Assistant Professor of Radiology who have always been encouraging and supportive during this study .

I wish to sincerely thank all my colleagues Dr. AL Periakaruppan, Dr. Arvinda, Dr. Amit, Dr. Saini, Dr. Santosh, Dr. Satya Narayan Patro, Dr. Somenath, Dr. Keerthiraj, Dr. Wangju, Dr. Mahadevaswamy, Dr. Uttam, Dr. Pranjal, Dr. Bhanuprakash, Dr. Swati and Dr. Deepak for their support at every step.

I am grateful to all our radiology technicians especially Mr. Hari Kumar, Mrs. Geetha, Mr. Alex, Mr. Johnson and Mrs. Sheeba for their wholehearted support at all times. I also thank all the DAMIT students with whom I have worked during this project.

I am grateful to the DSA lab staff - Sisters and the entire team who have been very cooperative to me all the time. I am also thankful to the entire staff of Radiology ward and the ICU for the patient care that they have provided at every step. I also thank the entire radiology staff and the hospital staff for their help. I also acknowledge the great help offered to me by all members of the medical records section.

I am grateful to all my patients who have always been cooperative, especially during interventions and from whom I learnt many important lessons during my residency.

I also acknowledge the constant support & encouragement from my entire family throughout my studies.

Dr. Milan B. Jolapara

ABBREVATIONS

APEH	-	Acute Postembolization Hemorrhage
ARUBA	-	A Randomised Multicenter Clinical Trial of Unruptured Brain Arterio-Venous Malformations
ASSET	-	Array Spatial Sensitivity Encoding Technique
AVF	-	Arterio-Venous Fistula
AVM	-	Arterio-Venous Malformation
BAVM	-	Brain Arterio-Venous Malformation
CENTRA	-	Contrast Material– Enhanced Robust-Timing Angiography
CT	-	Computed Tomography
DMSO	-	Dimethyl Sulfoxide
DSA	-	Digital subtraction angiography
ECM	-	Extracellular Matrix
EVOH	-	Ethylene-Vinyl Alcohol
GDC	-	Guglielmi Detachable Coil
IBCA	-	Isobutyl 2-Cyanoacrylate
LES	-	Liquid Embolic System
MMP	-	Matrix Metalloproteinases
MRA	-	Magnetic Resonance Angiography
MRI	-	Magnetic Resonance Imaging
mRS	-	Modified Rankin Scale
NBCA	-	N-Butyl 2-Cyanoacrylate
PVA	-	Polyvinyl Alcohol
SENSE	-	Sensitivity Encoding
SMC	-	Smooth Muscle Cells
TIE	-	Endothelial cell specific tyrosine kinase
TOF	-	Time of Flight
TRICKS	-	Time Resolved Imaging of Contrast Kinetics

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Introduction

INTRODUCTION

Brain arterio-venous malformations (BAVMs) are cerebrovascular anomalies, constituted by a complex, tangles web of afferent arteries and draining veins linked by an abnormal intervening vascular bed called nidus which may or may not harbour direct arterio-venous shunts[1]. BAVM represent one of the types within the spectrum of cerebro-vascular malformation phenotypes, which also includes cerebral cavernous malformations, capillary telangiectasias and developmental venous anomalies[2-4]. They are considered as congenital lesions representing inborn errors of embryonic vascular morphogenesis caused by defect or malfunction of embryonal capillary maturation process resulting in formation or persistence of arterio-venous shunts[5].

The prevalence of BAVM is not precisely known, but their incidence in general autopsy series is 0.15% and it has been estimated that between 0.14 and 0.8% of the population may present with BAVM in given year[3,6]. The incidence of symptomatic BAVM in the adult population is approximately one-tenth the frequency of intracranial aneurysms[3].

The main modes of clinical presentation of patients with BAVM include intracranial haemorrhage (45-50%), seizures (30%), headaches not

associated with haemorrhage (10-15%) and focal neurological deficits or other symptoms such as tinnitus (7-10%). In 5-8% cases they are asymptomatic and detected incidentally on neuroimaging investigation performed for other reasons[7,8]. It is the second most common cause of spontaneous intracerebral hemorrhage in an adult[9]. There is clear correlation between most of the clinical manifestations and specific angioarchitectural characteristics of the underlying BAVM, so that the presenting symptoms and the visualised angioarchitecture play a significant role in the indication and selection of the treatment modality or modalities in the individual patient[3,10].

Natural history of BAVM is only partially understood. It is found to be associated with an annual bleeding rate of 2-4% and annual rates of mortality of 1% and of severe morbidity of 1.7% [3, 9-13].

For the treatment of BAVM microneurosurgical, radiotherapeutical and endovascular techniques are applied either as single or combined techniques according to various selection criteria and grading systems[3]. Endovascular treatment of BAVM is aimed at either complete obliteration; or preoperative or preradiotherapeutical embolisation aiming at size reduction and hemodynamic improvement; or palliative embolisation aiming at partial and targeted elimination of angioarchitecturally weak elements or elimination of vascular elements responsible for venous hypertension or tissue hypoperfusion[3].

Since first BAVM embolisation in 1960 many embolic materials are used in embolization BAVM that includes Silastic spheres, balloons, silk, alcohol, PVA particles and cyanoacrylates[15-29]. Out of these liquid embolic agents N- butyl cyanoacrylate is most widely used and have shown good results[25-29]. In 1990 a new liquid embolic material called Onyx was introduced and Taki et al were the first to describe its use in BAVMs[30]. It is a nonadhesive liquid polymer made of mixture of ethylene- vinyl-alcohol copolymer and dimethyl sulfoxide. The theoretical advantage of a nonadhesive liquid is to eliminate the risk of gluing the microcatheter and subsequently to perform a more durable injection with larger amounts of agent delivered in single injection. Because of these properties, Onyx has become very popular and widely used embolic material[31-44].

Review of Literaure

REVIEW OF LITERATURE

CLASSIFICATION

PRIMARY CLASSIFICATION OF CEREBRAL ARTERIO-VENOUS VASCULAR LESIONS (ARTERIO-VENOUS SHUNTS)[45]

1. Single
    a. Micro- AV shunts (micro-AVM or micro-AVF)
    b. Macro-AV shunt (compartmented nidus or macro-AVF)
2. Multiple (nonfamilial)
    a. Metameric (Wyburn-Mason, cerebral-facial)
    b. Nonmetameric (multiple separate nidi or separate compartments within one nidus)
3. Multiple (familial)
    a. Systemic (Rendu-Osler-Weber or hereditary hemorrhagic telangiectasia)
    b. Nonsystemic (multiple separate nidi, with or without AVF)

TOPOGRAPHIC CLASSIFICATION OF BAVMs

Lasjaunias et al classified BAVMs into three groups based on its topographic location: 1) Lesions reaching the cortex, which includes cortical,

cortico- subcortical, cortico- ventricular and cortico- callosal lesions, 2) Deep-seated lesions and 3) Choroids plexus lesions[45].

ANGIOARCHITECTURE OF BAVMs

The term "angioarchitecture" refers to the angiographically demonstrable vascular elements composing a BAVM and includes the feeding arteries, the nidus, the draining veins, any associated vascular anomalies and secondary vascular changes induced by the inherent high-flow of the AVM, subsumized under the term high-flow angiopathy[46]. It is important to differentiate the primary abnormality (i.e. BAVM) from the host response to the presence of chronic shunting (i.e. arterial stenosis or aneurysms, venous stenosis or ectasias, non-sprouting angiogenesis)[45].

ARTERIES

Arterial feeders in BAVM are of two types. One is direct feeder that supply shunting area as a terminal branch. Other is indirect feeder, which supply shunting area en-passage, i.e., they predominantly supply normal territories and only secondarily supply the shunt[45]. They arise from the chronic sump effect of lesion. As the sump effect increases, indirect feeders can become more involved in AVM supply[45].

High flow in BAVM induces some changes in feeding arteries, which is referred as high-flow angiopathy. This includes arterial enlargement, arterial stenosis, flow related aneurysms and transfer of watershed[45,46].

Arterial enlargement is purely hemodynamic phenomenon, which stimulates natural channels to supply both the lesion and adjacent territories [45]. Stenosis of the feeding artery is also a part of high flow angiopathy. It occurs due to intra-luminal protrusion of endothelial cells and mesenchymal cell proliferation, resulting in intra-luminal stenosis [45].

Capillary proliferation (perinidal proliferative angiopathy) and watershed transfer are the part of findings constituting the high-flow angiopathy[45].

Association of arterial aneurysms and BAVM varies in different series from 2.7% to 51.5%[47,48]. It is the marker for increased risk for future hemorrhage[49]. Three types of arterial aneurysms associated with BAVM are a) flow-related aneurysms, b) intranidal aneurysms and c) dysplastic aneurysms[45]. Flow-related aneurysms occur on the pedicle supplying BAVM. They are of two types 1) proximal arterial aneurysm- located upstream, some distance away from the nidus and 2) distal or prenidal arterial aneurysm- located downstream, closer to the nidus[45]. According to literature, 37-82% of arterial aneurysms are flow related[50-52]. This includes ectasias and infundibula

>3mm in size[50,53,54]. Farther the aneurysm is located from the nidus, less likely it is the cause of hemorrhage and less likely it will regress following AVM treatment[45, 52, 55]. Intranidal aneurysms are more likely to present with hemorrhage compared to flow-related aneurysms (72% v/s 40%)[55]. Also in these cases rebleed rate is high[52]. Dysplastic or remote aneurysms develop on arterial branch independent from BAVM and hence are not considered flow related[50,56].

Dural supply to BAVMs could be attributed to its hemodynamic and angiogenic effects[45]. There are two types of dural supply: a) direct supply to BAVM through dural leptomeningeal anastomosis and b) indirect supply via anastomosis to normal cortical feeding arteries on way to BAVM[57, 58]. Both types can be induced by surgery, partial embolisation or subarachnoid hemorrhage[45].

NIDAL ANGIOARCHITECTURE

Nidus of BAVM is either compact or diffuse. In compact nidus BAVM there is absence of any intervening brain tissue. It may or may not be associated with intranidal arterio- venous fistulas[45]. In diffuse BAVMs there is presence of intervening brain tissue noted. They show less dominant but more numerous arterial feeders and veins draining them are almost normal in caliber with moderate transit time in the shunt. They may involve small area or large

area or entire hemisphere of the brain[45]. Nidus can be either single-compartmental or multi-compartmental[45].

Intranidal aneurysm can be either arterial or venous. It is difficult to distinguish them from arterial and venous pseudoaneurysms, which are the spaces within the unclotted portion of the hematoma[45]. Presence of intranidal aneurysms is associated with increased risk of future hemorrhage[52]. Intranidal pseudoaneurysms are usually found during the acute stage of intracerebral hematoma. They are associated with increased risk of rerupture[52].

VEINS

A separate vein will drain each of the compartments of the nidus[46]. Drainage of BAVM can be either in superficial (cortical) or deep venous system. Drainage in deep venous system increases the risk of hemorrhage[45,46,59)]

As for arteries, draining veins also undergo high-flow angiopathic changes, which include venous stenosis/ occlusion, sinus stenosis/occlusion and venous varix/ ectasias[45, 46].

Direct shunting of blood at arterial pressure causes dilatation and tortuosity in the involved veins. Stenosis or thrombosis of draining veins or sinuses can occur resulting in increased proximal venous pressure and

secondary venous varix formation. Also presence of high flow shunt can cause venous reflux into the veins draining normal brain parenchyma[45, 46].

EPIDEMIOLOGY

PREVALENCE

The prevalence of BAVM in general population is uncertain and is probably influenced by geographical and racial factors. Also because of the rarity of the disease and the existence of asymptomatic patients, establishing a true prevalence rate is difficult and probably not feasible[60]. It has been reported to be ranging form 0.02% to 0.11% from different places[6,61,62]. Berman et al (2000) reviewed all the relevant original literature and concluded that the most reliable estimate for the occurrence of disease is the detection rate for symptomatic lesions: 0.94 per 100,000 persons per year[63].

INCIDENCE

The incidence, i.e. the frequency of newly diagnosed BAVM per year, has been estimated to be 0.001-0.01%[64-66].

DEMOGRAPHIC CHARACTERISTICS

Mean age of presentation of BAVM is between 30 to 40yrs[67]. There is no sex predominance noted[67].

CLINICAL PRESENTATION

The lobes of brain involved in arterio-venous malformation did not influence the mode of presentation. Clinical features of BAVM depend on its angioarchitecture[64]. Autopsy data had showed that only 12% of AVMs become symptomatic during life[68].

Haemorrhage

Intracranial haemorrhage is the most common clinical presentation of BAVM, with a frequency of 30% to 82%[11]. It has been postulated that sudden headaches, with or without seizures, and other acute symptoms (often transient) can be considered as minor expressions of local haemorrhages[69]. Reported annual bleeding rate is 2-4% regardless of initial clinical presentation[65, 70]. Ruptured BAVMs have increased risk of rebleeding (6%) in the first year after hemorrhage, which decrease to baseline after one year[70]. The first haemorrhage is associated with mortality of 10%, reaching up to 20% for subsequent recurrent haemorrhages[71]. Formula for lifetime risk of bleeding is, 105 – age in years = risk of bleeding.

There is statistically significant increased incidence of haemorrhage in AVMs that are associated with flow-related aneurysms, stenosis or occlusion of draining veins, deep venous drainage or that are located in deep parts of brain, in posterior fossa and temporal lobe[45,46,59,64,72,73].

It has been postulated that small and micro-AVMs are associated with higher risk of haemorrhage compared to larger AVM[70,74]. However, later reports suggest that there is no direct correlation between size of AVM and incidence of haemorrhage[62,64,65,71,75].

The feeding artery pressure was higher in patents presenting with haemorrhage[76]. Yasargil (1987) found the venous pressure in ruptured AVMs to be higher than nonruptured ones[77].

Seizures

Seizures are the second most frequent presenting symptoms, reported to occur in 28-67% of BAVM patients[56,62]. It occurs due to venous hypertension, raised intracranial pressure or due to mass effect of enlarged veins[45,62].

Headache

Headache not associated with acute haemorrhage is relatively frequent symptom and is presenting symptom in 7% to 48% of cases, with a mean of 31%[78]. Dural as well as posterior cerebral artery supply to a BAVM is known to be potentially responsible for headaches[45,46,62].

Focal neurological deficits

Focal neurological deficit without haemorrhage is the presenting complains in 1% to 40% of the patients[79]. It may be caused by several

mechanisms including venous hypertension, mass effect caused by compression of brain parenchyma by venous ectasias or varices, decreased perfusion because of associated arterial stenosis or steal effect of AVM [45,62].

PATHOLOGY

Macroscopically, BAVM is composed of (a) clustered and abnormally muscularized feeding arteries, which may also show changes such as duplication or destruction of the elastica, fibrosis of the media, and focal thinning of the wall; (b) arterialized veins of varying size and wall thickness; (c) structurally ambiguous vessels formed, solely of fibrous tissue or displaying both arterial and venous characteristics; and (d) intervening gliotic neural parenchyma[6,80-82].

PATHOGENESIS

BAVMs are generally regarded as congenital lesions, representing inborn errors of embryonic vascular morphogenesis, caused by defect or malfunction of embryonal capillary maturation process and resulting in the formation or persistence of arterio-venous shunts[5]. Majority of BAVMs (exception Vein of Galen Malformation) develop postnatally and represent complex endothelial cell dysfunction, triggered by still unknown factors[83].

The altered expression of up to 900 genes has been associated with AVMs[84]. Perhaps > 300 genes are up-regulated and almost 560 are down-regulated in cerebral vascular malformations[85]. These genes encode growth factors, cell adhesion and extracellular matrix (ECM) factors, inflammatory factors, matrix metalloproteinases (MMPs), and endocrine hormones. Different cell types, including endothelial cells, vascular smooth muscle cells (SMCs), and inflammatory cells, have been examined to understand the pathogenesis of BAVMs[86].

Different chemical and molecular factors involved in pathogenesis of BAVM includes Vascular endothelial growth factor subtypes A-E, placental growth factor, Transforming growth factor- α and β, b-fibroblast growth factor, angiopoietin-1 (TIE2 agonist), angiopoietin-2 (TIE2 antagonist), delta, endoglin, neuropilin and ephrin[86].

The hypoxic environment surrounding the brain AVM is thought to stimulate the secretion of all the above-mentioned angiogenic factors and their levels of activity[86].

Integrins, immunoglobulins, cadherins, and selectins, along with the ECM milieu, may have significant effects on angiogenesis, vasculogenesis, and brain AVM growth[86]. Integrin $\alpha_v\beta_1$ and $\alpha_v\beta2$ and matrix

metalloproteinases (especially MMP-9) are found to be strongly associated with BAVM formation and growth[86-89].

Endothelial cells plays fundamental role in vasculogenesis, angiogenesis and vascular remodelling and its turnover is found to increased significantly in BAVM[90-92]. Abnormal assembly or differentiation of vascular smooth muscle cells is also involved in pathogenesis of BAVM[93].

Consistent with increasing evidence implicating inflammation in the pathophysiology of BAVM, recent studies of promoter polymorphisms in inflammatory cytokine genes have found that promoter polymorphisms in IL-1, IL-6, tumor necrosis factor– α and apolipoprotein E2 is associated with BAVM susceptibility as well as risk of intracranial hemorrhage[94].

The role of dysregulated apoptosis has been found to be associated with BAVM growth[86].

DIAGNOSTIC IMAGING

CT scan is usually the first imaging modality used, mainly to rule out haemorrhage in patients with a sudden-onset of a neurological deficit[95]. CT angiography helps in diagnosis of vascular abnormalities in patients with intraparenchymal hemorrhage[96,97]. However, it doesn't provide the temporal

information. Use of mobile CT during AVM embolisation may help in preventing inadvertent embolisation of normal territory[98].

MRI helps in specific diagnosis of BAVM and provides good anatomical delineation of AVM nidus and its relationship to vital cerebral structures. It also shows associated haemorrhage and other parenchymal changes. MRA is of value in providing three-dimensional representations of AVM vascular architecture[99]. Three-dimensional dynamic time resolution-contrast enhanced MRA technique using combination of parallel imaging technique (ASSET: array spatial sensitivity encoding technique) and time resolved method (TRICKS: time resolved imaging of contrast kinetics) on 1.5Tesla MRI provide subsecond and submillimeter resolution and could become the first line investigation technique in diagnosis and follow-up of BAVMs[100]. Other techniques of dynamic imaging of BAVM includes four-dimensional radial acquisition contrast-enhanced MRA at 3Tesla; time-resolved magnetic resonance angiography with sensitivity encoding (SENSE) in combination with keyhole acquisition and contrast material– enhanced robust-timing angiography (CENTRA) k-space sampling techniques at 1.5 and 3Tesla[101-103]. Three-dimensional TOF MRA at 3Tesla is superior to same technique at 1.5 Tesla in evaluation of BAVM[104]. Functional MRI has demonstrated that aberrant mapping of cortical functions can occur in presence of an AVM that is situated in expected location of primary sensorimotor

cortex, implying neural plasticity in response to the physiologic impact of AVMs[105,106]. Diffusion tensor imaging is used to study the modification of white matter tracts in patients with AVMs[107].

Angiography is the gold standard for diagnosing AVM and to make a decision regarding the treatment [108]. Superselective angiography gives a more detailed analysis of the AVM angioarchitecture like intranidal aneurysms, direct arteriovenous fistulas and the compartments of the AVM and their venous drainage[108]. AVM nidus size is measured in the arterial phase of the angiogram till the first draining vein starts appearing[108]. Three-dimensional rotational digital subtraction angiography may help in better delineation of AVM nidus[109]. Three-dimensional rotational DSA using superselective microcatheterization helps in demonstrating different compartments of BAVM nidus[110].

TREATMENT

The discovery of a BAVM in a patient is not necessarily an automatic indication for treatment[3,46]. The primary goal of treatment of BAVM is to prevent new or recurrent haemorrhage. Other goals include improving or stabilizing neurological deficits, to treat intractable epilepsy or to reduce the severity and frequency of chronic headaches[3,46].

Modern treatment of arteriovenous malformations of the brain includes the following interventions alone or in combination: endovascular embolization, microsurgical resection, and stereotactic radiotherapy[3,46].

SURGERY

Surgery alone should only be recommended when complete excision can be accomplished with reasonable risk[3].

Spetzler and Martin classified BAVMs according to their degree of surgical difficulty and the risk of surgical morbidity and mortality[111].

Table 1: Spetzler-Martin Grading of BAVM

Graded feature		Points
Size	Small(<3cm)	1
	Medium (3-6cm)	2
	Large(>6cm)	3
Eloquence	Non-eloquent	0
	Eloquent	1
Venous drainage	Superficial	0
	Deep	1

The sum of the three scores provides the AVM grade, which may range between Grade I and V. In addition, large AVMs that involve extensive areas

of eloquent cortex or smaller AVMs located within the brain stem or hypothalamus are classified as Grade VI and are regarded as inoperable[112].

Microsurgical resection is preferred for treatment of AVMs in resectable areas[113-115]. Hamilton and Spetzler showed no permanent deficits in Spetzler-Martin Grade I-III patients[116].

RADIOTHERAPY

Radiotherapeutical treatment of small (<3cm) AVMs has also shown good obliteration rates at 3 years[117]. But due to long latency period, radiotherapy alone should be reserved for the lesions not accessible to endovascular or surgery[3].

EMBOLIZATION

Goal of embolisation is primarily curative. However, in some cases the goal is either partial (targeted) embolisation or palliative embolization or preoperative/preradiotherapy embolisation.

The Spetzler-Martin grading system does not correlate with the difficulty of treating patients with AVMs by endovascular approach and cannot be applied to predict the risk of neurological impairment resolution from endovascular treatment[45,46]. It does not take into consideration the possible displacement of functional (eloquent) territories in response to the

presence of the AVM. Also it does not recognize the individual characteristics of AVM in a given patient (associated aneurysms, etc.); nor does it recognize that surgical high-grade AVM is not necessarily a dangerous one for the patient[45].

Partially (targeted) embolisation is aimed at correcting the disequilibrium between host (patient) and AVM that is responsible for symptoms. Proper understanding of clinical-angioarchitecture relationships is must for this. Also both clinical and imaging follow up is needed to verify the achieved result[3].

Partial (palliative) embolisation is performed in patients presenting with progressive neurological deficit and having large and deeply located AVMs that cannot be cured by current technology. Embolization should be focused on occlusion of largest shunts within the nidus to decrease venous hypertension[3].

Curative embolization refers to complete anatomical obliteration of the malformation by endovascular route[3]. Results reported to date, on the rate of total occlusion of brain AVMs with embolization, range from 0 to 53.9%[28-44,46].

Preoperative embolization is done to eliminate deep feeding arterial supply, to occlude intranidal arterio-venous fistula and to reduce overall size and flow through the nidus[3,46].

The purpose of embolization prior to stereotactic radiotherapy can be either to reduce the size of AVM to make it amenable to radiotherapy or to eliminate angioarchitectural weaknesses to decrease risk of haemorrhage during latency period of radiotherapy[3,46].

A Randomised Multicenter Clinical Trial of Unruptured Brain AVMs (ARUBA) is a prospective, multicenter, parallel design, randomised, controlled trial whose primary objective is to determine whether medical management improves long-term outcomes of patients with unruptured BAVMs compared to interventional therapy (with endovascualar procedures, neurosurgery, or radiotherapy, alone or in combination). The results of this study are still awaited[118].

HISTORY OF ENDOVASCULAR EMBOLIZATION OF AVMS

Luessenhop and Spence (1960) were the first to perform embolization of BAVM using steel particles (spheres) covered with methyl methacrylate introduced into the surgically exposed internal carotid artery[14]. This was followed by use of barium- impregnated Silastic spheres introduced into the

cerebral circulation through a catheter inserted surgically into the common carotid artery and advanced manually into the internal carotid artery[119-121].

In 1964 Dolace reported first superselective catheterisation of the cerebral arteries using self-constructed microcatheter, inserted percutaneously with Seldinger technique into internal carotid artery and advanced into the proximal anterior and middle cerebral arteries[122]. Then in late sixties, Yodh et al (1968) and Hilal (1969) used magnetic control system with Silastic catheters for distal microcatheterization, but without success[123,124]. In 1972 Kricheff et al developed percutaneous transfemoral catheter embolization technique, which enabled either the anterior or the posterior cerebral circulation to be approached[125]. This nonselective endovascular technique using flow-directed particles was applied palliatively for embolization of large BAVMs or preoperatively[125,126].

Major technical breakthrough in endovascular techniques occurred in 1974, when Serbinenko reported for first time on introduction of detachable balloons mounted on tip of microcatheters and used for flow-guided intracranial navigation beyond the circle of Willis for occlusion of major cerebral arteries as well as of feeding arteries related to brain AVMs and AV-fistulae[15]. This had major impact on further refinement of cerebral endovascular techniques leading to modern era of superselective microcatheterization and embolization[17,18,127].

Kerber (1976) introduced flow-guided, calibrated-leak microballon catheter systems, permitting superselective microcatheterization of brain AVM feeding arteries and embolization with acrylics[17]. Pevsner (1977) introduced a pressure chamber to enhance the propulsion of the calibrated-leak microballoon-catheter and Berenstein (1981) and Debrun et al (1982) introduced calibrated-leak latex balloons to improve small vessel microcatheterization and acrylic delivery[18,128,129]. This technique was in routine use until 1986/87, when a new era of superselective cerebral vascular navigation began with the introduction of the newest generation of variable stiffness microcatheters, used either in conjunction with microguidewires[130] or as flow-guided systems[131] and permitting safer and more controllable superselective catheterization.

At the beginning of the 1990s, many authors reported results of preoperative embolization with polyvinyl alcohol (PVA) particles[19-22]. Microcoils were also used to treat brain AVMs in order to increase the effectiveness of occlusion by PVA[22]. The main advantage of preoperative PVA embolization was that the AVM is easily compressed and retracted at surgery[19]. However, its use was associated with high recanalization rate and histologically a moderate foreign body reaction with areas of focal angionecrosis was observed following PVA embolizaton[132]. Wallace et al (1995) and DeMeritt et al (1995) demonstrated the superiority of NBCA over PVA as embolic agent in endovascular treatment of BAVMs [29,133].

Other agents have also been used for brain AVM treatment, such as silk sutures[23], pure ethanol[24] or ethibloc[134].

Cyanoacrylates were first used in 1970s for preoperative embolization[25-29, 135]. Original clinical experience was gained with a vinyl monomer of the alkyl 2-cyanoacrylates, isobutyl 2-cyanoacrylate (IBCA)[25, 135-140]. This agent became unavailable by the late 1980s and was replaced by a similar compound, N-butyl 2-cyanoacrylate (NBCA)[141-143]. Brothers et al (1989) and later Berenstein and Lasjaunias (1991) and Debrun et al (1997) showed significant advantages of NBCA over IBCA. NBCA has a lower bonding strength, higher surface tension and higher viscosity than IBCA[62,141,144]. At present, NBCA can be obtained under the name Histoacryl (Braun, Frankfurt, Germany) and Trufill (Cordis Endovasuclar, Miami Lakes, FL, US). A similar preparation was marketed under the name Avacryl (Tripoint Medical, Raleigh, NC) but was withdrawn from medical use in 1992. In 2003 new liquid acrylic glue Glubran 2 (GEM Srl, Viareggio, Italy) was introduced. It had been shown in experimental works and clinical study that Glubran does not produce bubbles and seems to diffuse more homogenously and in more predictable way than Histoacryl[145-147].

Before 2005, the most commonly used embolic agent for AVM treatment was the fast polymerizing liquid adhesive NBCA. The use of NBCA in brain AVMs requires experience and skill because intranidal flow and polymerization of NBCA are quick and largely unpredictable[31,38,148].

Taki et al were the first to describe Onyx for embolization of cerebral AVMs in 1990[30]. In 1994 Chaloupka et al and in 1996 Sampey et al described toxic effect of DMSO to the arterial wall[149,150]. Later Murayama et al and Chaloupka et al demonstrated absence of toxic effect of DMSO in animal experiments, when injected in low dose and at slower rate[151,152]. Jahan et al described the injection protocol in a series of 23 patients with total 129 pedicles treated. This article emphasized the critical need for slow and controlled injection of solvent DMSO[31]. From then till now Onyx has emerged as embolic material of choice in embolization of BAVM[32-44]. Because of increased obliteration rate achievable with Onyx, the goal of embolization has shifted from preoperative or preradiotherapy to curative embolization[40,43].

Also since early 1980s with introduction of digital subtraction technique in cerebral angiography, there has been significant progress taken place in imaging including full implementation of structural, functional, vascular-luminal, perfusion and diffusion MR throughout 1980s and 1990s for pretherapeutic evaluation, precise topographic localization and post-treatment follow-up of BAVMs; and introduction of bi-plane neuroangiographic equipment in mid- 1990s with simultaneous bi-plane fluoroscopic and road-map capabilities[46, 153].

Aims & Objectives

AIMS AND OBJECTIVES

Aim of this study was to evaluate role of Onyx in endovascular treatment of BAVM. This includes

1. To analyse the results of endovascular embolization of BAVM using Onyx.
2. To evaluate technical aspects associated with Onyx embolization of BAVM.
3. To evaluate the complications associated with Onyx embolization of BAVM.

Materials & Methods

MATERIALS AND METHODS

PATIENTS DEMOGRAPHICS

This is the retrospective and prospective study of all the patients with BAVM who were treated in our institute with onyx with or without other embolic agents since its first use in February 2006 till August 2009. Total 44 patients have undergone embolization with onyx during this period. Out of these 20 were females and 24 males with mean age of 27.66 yrs (range 7-49yrs).

MATERIALS USED

ONYX

Description:

- Onyx (eV3, Irvine, California) is a non-adhesive liquid embolic agent comprised of EVOH (ethylene vinyl alcohol) copolymer dissolved in DMSO (dimethyl sulfoxide), and suspended micronized tantalum powder (35% wt/vol) to provide contrast for visualization under fluoroscopy.

- The Onyx Liquid Embolic System (LES) consists of a 1.5 ml vial of Onyx, a 1.5 ml vial of DMSO, and two 1 ml Onyx delivery syringes and one DMSO syringe.

- Onyx is available in four product formulations, Onyx 18 (6% EVOH), Onyx 20 (6.5% EVOH), Onyx 34 (8% EVOH) and Onyx 500 (20% EVOH). Onyx 18 will travel more distally and penetrate deeper into the nidus due to its lower viscosity compared to Onyx 20, similarly Onyx 20 is less viscous than Onyx 34 and Onyx 500 is most viscous. Numbers 18, 20, 34 and 500 denotes viscosity in centipose (unit of viscosity).

- Final solidification occurs within five minutes, for all product formulations.

- The vials are kept on a shaker (Vortex Genie; Scientific Industries, Bohemia, NY) for at least 20 minutes to ensure proper mixing of the tantalum powder.

- Onyx 18 is used for embolization of a plexiform nidus, Onyx 34 is used for embolization of large arteriovenous shunts in the AVM and Onyx 500 is used for embolization of aneurysms.

- DMSO is potentially angiotoxic, but this effect is considered negligible if used at the recommended infusion rates of 0.16ml/min (0.25ml/90sec)[31, 149-152].

- The DMSO compatible delivery microcatheters that are indicated for use in the neurovasculature are Marathon, UltraFlow HPC, Echelon, Rebar and Sonic microcatheters.

- Ultraflow HPC (eV3, Irvine, CA) and Marathon (eV3, Irvine, CA) microcatheters are 165 cm long, having internal diameter of 1.5F and 1.3F respectively and a minimum dead space of 0.26 ml and 0.23 ml respectively. Their respective proximal outer diameter is of 3F and 2.7F and distal outer diameter of both catheters is 1.5F. These catheters are compatible with hydrophilic microguidewires like Transcend 0.010" and Mirage with a maximum outer diameter of 0.010" and 0.008". It is recommended that a guiding catheter with a minimum internal diameter of 0.053" (1.35mm) to be used with these microcatheters.

- Echelon (Microtherapeutics, Irvine, CA) microcatheter is 150cm long, having internal diameter of 0.43mm (0.017"), outer diameter of 0.7mm (2.1F) proximally and 0.57mm (1.7F) distally with minimum dead space of 0.34 ml; allowing maximum guidewire of 0.014". Rebar (Microtherapeutics, Irvine, CA) is 153cm long microcatheter, having

inner diameter of 0.53 (0.021"), outer diameter of 0.91mm (2.7F) proximally and 0.81mm (2.4F) distally with minimum dead space of 0.49 ml; allowing maximum guidewire of 0.018".

- Sonic (Balt Extrusion, Montmorency, France) is a flow-directed braided microcatheter with Fusecath system, which limits the consequences of the distal part sticking in the embolization product. With a moderate traction, the tip of the Sonic will come away from the rest of the catheter. Sonic is available as 1) Sonic 1.2F15 with fusecath length of 1.5cm, total length of 165cm, distal tip external diameter 1.2F and internal diameter 0.17mm, dead space of 0.3ml, maximum reflux allowed 2cm; 2) Sonic 1.2F25 with fusecath length of 2.5cm, total length of 165cm, distal tip external diameter 1.2F and internal diameter 0.17mm, dead space of 0.3ml, maximum reflux allowed 3cm; 3) Sonic 1.2F25.180 with fusecath length of 2.5cm, total length of 180cm, distal tip external diameter 1.2F and internal diameter 0.17mm, dead space of 0.38ml, maximum reflux allowed 3cm; and 4) Sonic 1.5F25 with fusecath length of 2.5cm, total length of 165cm, distal tip external diameter 1.5F and internal diameter 0.27mm, dead space of 0.33ml, maximum reflux allowed 3cm. Sonic comes with microguidewire: Steel007 for 1.2F and Steel008 for 1.5F microcatheter.

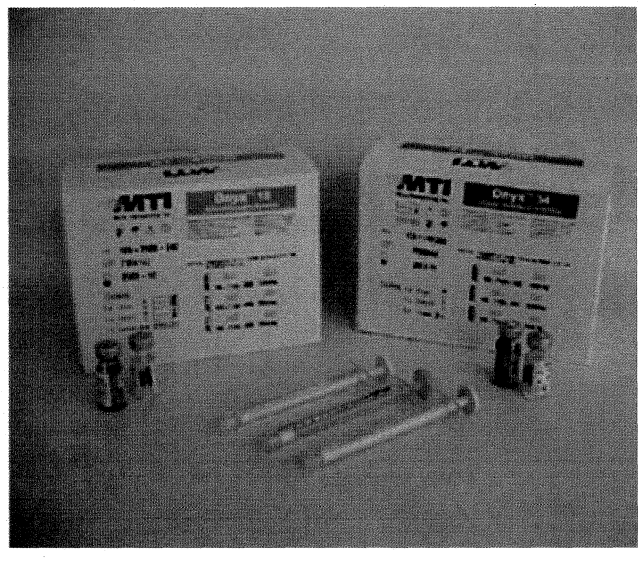
- Transcend 0.010" (Target, Boston Scientific, Fremont, CA) is a hydrophilic microguidewire having total length of 205 cm and maximum outer diameter of 0.010". Mirage (eV3, Irvine, CA) is also hydrophilic microguidewire having total length of 200 cm and maximum outer diameter of 0.012" proximally and 0.008" distally.

Principles of action:

- Onyx is delivered by slow controlled injection through a microcatheter into the brain arterio-venous malformation under fluoroscopic control. The DMSO solvent dissipates into the blood, causing the EVOH copolymer and suspended tantalum to precipitate *in situ* into a spongy, coherent embolus. Onyx immediately forms a skin as the polymeric embolus solidifies from the outside to the inside, while traveling more distally in the lesion. This process begins on the surface while the core is still liquid, resulting in a soft, and nonadherent mass. Therefore, Onyx has a lava-like flow pattern within blood vessels without any fragmentation during the injection. Due to these properties and because Onyx is not absorbable, it is capable of producing permanent occlusion of the nidus of the AVM[39, 151].

- Once microcatheter is wedged into the Onyx cast around the tip of catheter, several compartments of the nidus can be embolized from a single catheter position[39].

- Because of the nonadhesive properties of Onyx, the injection can be interrupted to assess the progress of the embolization and can then be continued[39].



EMBOLIZATION PROCEDURE

- All embolization procedures were performed with the patient under general anesthesia.

- All procedures were performed in single planer cath-lab (GE Advantx DLX-LCV DSA suite with C-arm, Milwaukee, USA).

- Systolic blood pressure during the procedure was controlled at 90-100 mmHg. Postembolization, the blood pressure was kept at 90-100 mmHg after the procedure for 24 hours.

- When it was planned to use onyx, the vials were kept on a shaker (Vortex Genie; Scientific Industries, Bohemia, NY) to ensure proper mixing of the tantalum powder.

- Catheterization was performed by a transfemoral approach using standard coaxial techniques.

- An intravenous bolus of 2500IU of heparin was given to each patient after puncture and 1000IU hourly thereafter.

- A 4-vessel cerebral angiography was performed and the feeders to be embolized were decided.

- A 6F-guiding catheter (Launcher balanced guide catheter, Meditronic Inc., Minneapolis, MN, USA; Vistabrite, Cordis, Miami Lakes Fla; or Envoy guiding catheter, Cordis Neurovascular, Miami Lakes, Fla) was then inserted in either distal cervical internal carotid or distal V2 segment of dominant vertebral artery depending on the feeders to be embolized.

- Then microcatheter (Ultraflow HPC or Marathon) was taken as close to the nidus as possible with the help of microguidewire (Transcend 0.010" or Mirage). The microguidewire was then removed, and a superselective angiogram was performed via the microcatheter.

Onyx injection technique:

- In all cases Onyx 18 was used. Microcatheter was advanced superselectively in to the feeder to be embolized. Prior to injecting the Onyx we performed multiple micro-angiographies from more proximal locations (3-4cm proximal to the embolization point) with the aim of identifying any branches arising from that segment that supplied normal brain and should not be occluded by the reflux of Onyx along the microcatheter.
- When a clear pedicle was identified we performed micro-angiographies from the embolization point in order to visualize the portion or compartment of the nidus that was filling and to be embolized with Onyx.
- When we were satisfied that we understood completely the anatomy of the supplied area, we proceeded with the injection of Onyx.
- The microcatheter was flushed with 8 ml of normal saline using 1ml leurlock syringe.
- 1 ml DMSO was aspirated into the yellow MTI DMSO 1 ml syringe.

- DMSO (Dimethyl Sulfoxide) was injected slowly at the recommended rate of 0.16 mL/min (0.25 mL/90 sec) to fill the dead space of microcatheter (0.26ml and 0.23ml for Ultraflow HPC and Marathon microcatheter respectively). DMSO was also used to wash the hub of the syringe.

- DMSO syringe was left attached to the microcatheter until Onyx is ready to deliver.

- 1ml Onyx was aspirated into a white MTI Onyx 1 ml syringe.

- Meniscus-to-meniscus connection was made between the Onyx (in the syringe) and the DMSO (in the catheter hub). Onyx syringe was connected immediately to microcatheter hub to prevent air entry. The syringe was held vertically with the tip pointing downwards on connection, after which it was immediately turned over 180° so that its tip is pointing upwards and then the injection was started directly. This manoeuvre ensured a sharp interface distinctly dividing the DMSO from the Onyx inside the catheter.

- Onyx was slowly injected at the recommended slow and steady rate of 0.16 mL/min (0.25 mL/90 sec) to fill the microcatheter and replace the DMSO in the dead space.

- The embolic agent was released at the tip of the microcatheter under free-flow conditions and filled the directly dependent nidus compartment

antegradely, and subsequently refluxed into the feeding artery beyond the tip of microcatheter (first penetration).

- The goal was to form a cast of Onyx around the tip of the microcatheter over a short distance, so that when Onyx was injected, it would flow forward into the AVM and not retrograde into the feeding vessel.

- When the reflux was noted along the microcatheter, the injection was stopped for 2 min to allow the Onyx to partly solidify.

- Subsequently Onyx was injected in a very small volumes with 2 min waiting periods between injections; this allowed the material to fill the empty spaces in the reflux and, thereby, to create a "plug". The "plug" was usually solid enough within 10-15min to oblige the material to advance distally (second penetration of the nidus).

- The embolization was then continued until we visualized Onyx entering a venous part of the AVM. This was identified directly as a vascular space that had a diameter that was significantly larger than the arterial feeder or indirectly when we visualized Onyx flowing rapidly in a straight line without branching or laminating along the venous wall. In these instances, we stopped the injection for 2 min and repeated the sequence of very small volume injections and 2 min waiting periods until the Onyx advance into different part of nidus.

- The injection rate of Onyx never exceeded 0.3ml/minute.

- Very frequently, Onyx entered a different compartment of the nidus that was not seen filling during superselective angiograms from the embolization point.

- Using these intracompartmental communications of the nidus we were very often able to embolize larger part of nidus from one feeding pedicle. The embolized part of the nidus was larger than the one documented by the pre-embolization superselective angiogram.

- The embolization from the specific pedicle was terminated when all forward advancement led into venous spaces or the length of the proximal plug reached 1.5 cm.

- Following a 2 min waiting period starting after the last injection, the micro-catheter was removed as follows: the microcatheter was pulled back slowly, increasing the tension on the tip during withdrawal, holding the tension for a few seconds. This manoeuvre was repeated for few times until the microcatheter pulled out of the cast of onyx around it.

- After completion of embolization check angiogram was taken.

- Post-procedure patient was kept in intensive care unit for 24-48 hrs, then shifted to ward and then discharged on 4^{th} day.

FOLLOW UP

- Patients were clinically followed up at 3months, 6months, 1year and then yearly thereafter.

- Follow up imaging was done at 6months and/or 1year and then depending on the results achieved. Follow up imaging was done with either MRI with contrast-enhanced MRA or with DSA.

- However in individual patients, frequency of clinical and imaging follow-up was tailored as required.

Following data was acquired for each patient[154]:-

PATIENT DETAILS

Age at presentation

Sex

CLINICAL PRESENTATION

Hemorrhage

Seizure

Focal neurological deficit

Headache

Other symptoms

Similar episode in childhood

Modified Rankin scale

IMAGING

AVM number

AVM location

AVM size (Antero-Posterior) x (Right to Left) x (Supero-Inferior) mm, Volume in ml

Eloquence of site of AVM

ANGIOGRAM/ ANGIOARTITECHTURE

Arterial supply

Feeding arteries

Dural feeders-

Arterial aneurysm- Flow related (proximal/ distal/ nidal) or Dysplastic

Transfer in watershed

Arterial enlargement

Arterial stenosis

Nidus

Compact or Diffuse

Number of compartments

Intranidal arterio-venous fistula

Intranidal aneurysm

Venous drainage

Superficial or Deep or Both

Periventricular drainage

Number of draining veins leaving nidus

Number of veins reaching sinus

Converging or Diverging system

Venous stenosis or occlusion

Sinus thrombosis / Occlusion

Venous ectasia (dilatation)

Venous varix

Venous reflux

SPETZLER-MARTIN GRADE

PROCEDURE

Microcatheter used

Microguidewire used

Number of feeders embolized with onyx

Amount of onyx (ml) injected in each feeder

Time of onyx injection (mins) in each feeder

Number of feeders embolized with other embolic material

Number of feeders embolized per session

Number of sessions per patient

Total duration of treatment in months

Percentage obliteration immediately at end of last embolization procedure-Total (100%)/ Near total (>90%)/ Subtotal (>50%)/ Partial (< or =50%)

Treatment is completed or not completed

FOLLOW UP

Clinical follow up period in months

Modified Rankin scale at the time of last clinical follow up

mRS improved/ worsen/ remained same
Death

Angiographic follow up period in months

Percentage obliteration at the time of last angiographic control- Total (100%)/ Near total (>90%)/ Subtotal (>50%)/ Partial (< or =50%)

Increase/ decrease/ no change in size of nidus compared to last embolization

COMPLICATIONS

Hemorrhagic

Ischemic

Others

Temporary

Permanent

Death

Technical complications- microguidewire perforation

Microcatheter gluing after onyx injection- Time of injection in mins, Amount of reflux allowed in mm, microcatheter was cut or got broken.

Results

RESULTS

PATIENT CHARACTERISTICS:

Total forty-four patients with BAVMs were embolized in our institute with Onyx with or without other embolic material. Mean age of the patients was 27.66 yrs (range 7-49yrs). Out of these 20 (45.5%) were females and 24 (54.5%) were males with no significant sex preference.

Most common presenting symptom was intracranial haemorrhage (36.4%, 16/44 patients). This was followed by seizures (34.1%, 15/44 patients), headache (20.4%, 9/44 patients) and focal neurological deficit (9.1%, 4/44 patients). Six (13.6%) patients gave history of similar episodes in past. Of these six patients four presented with haemorrhage, one with seizures and one with focal neurological deficit.

Table 2: Presenting symptoms of patients with BAVMs

Presenting symptoms	No: of patients	Percentage (%)
Hemorrhage	16	36.4
Seizures	15	34.1
Headache	9	20.4
Focal neurological deficit	4	9.1
Total	44	100

BAVMS:

Of 44 patients 3 AVMs were located in infratentorially (6.82%) and remaining 41 supratentorially (93.18%); 26 (59.1%) on left and 18 (40.9%) on right. Of 41 supratentorial BAVMs, 3 were deep-seated (7.32%), while 38 were hemispheric (92.38%). Following table shows the location of BAVMs:

Table 3: Location of BAVMs

Location	No: of patients	Percentage (%)
Frontal	8	18.2
Parietal	7	15.9
Temporal	6	13.6
Occipital	4	9.1
Fronto-Parietal	8	18.2
Parieto-Occipital	1	2.3
Temporo-Occipital	4	9.1
Thalamus	1	2.3
Choroid plexus	2	4.5
Brainstem	1	2.3
Cerebellar	2	4.5
Total	44	100

According to topographical classification 23 BAVMs were cortico-subcortical (52.3%), 15 cortico-ventricular (34.1%) and 2 (4.5%) cortico-callosal, deep-seated and choroid plexal each. Twenty-six (59.1%) of BAVMs treated were located in eloquent areas of brain and eighteen (40.9%) in non-eloquent areas.

Size of the BAVMs treated ranged from 1.87ml to 115.5ml (mean 18.19ml). Nineteen (43.2%) were <3cm, 22 (50%) 3-6cm and 3 (6.8%) >6cm in largest diameter.

Table 4: Size of BAVMs

Size	No: of patients	Percentage (%)
< 3 cm	19	43.2
3-6 cm	22	50
> 6cm	3	6.8

Forty (90.9%) patients had compact nidus BAVMs while remaining four (9.1%) patients had diffuse BAVMs. Number of compartments in compact nidus BAVMs ranged from one to three (mean 1.85).

High-flow angiopathic changes were noted in feeding arteries. Transfer of watershed was noted in 10 (22.7%) patients. Feeding artery enlargement was noted in all cases. Feeding artery stenosis was noted in 9 (20.5%) cases. Total 13 (29.55% of all BAVMs) arterial aneurysms were found in twelve

patients. All of these were flow-related; three proximal, three distal and seven nidal arterial aneurysms. One patient had two arterial aneurysms, one proximal and one nidal. Intranidal aneurysm (or pseudoaneurysm) was present in four (9.1%) cases. Intranidal arterio-venous fistula was noted in four (9.1%) cases. Dural arterial supply was noted in 10 (22.73%) of these malformations. Out of these, five showed presence of dural supply on first angiogram, while other five showed development of dural supply on follow up angiograms after embolization. Of the five that showed dural supply on first angiogram, four had not undergone any treatment before angiogram while fifth patient had undergone surgical evacuation of hematoma before angiogram. Posterior cerebral artery supply was seen in 21 (47.7%) of patients.

In 18 (40.9%) cases of BAVMs venous drainage occurred exclusively in superficial venous system, in 4 (9.1%) cases it was exclusively in deep venous system, while in 22 (50%) patients, BAVMs drained into both superficial and deep venous system. Periventricular venous drainage was noted in 13 (29.5%) patients. Convergence of veins draining the nidus was found in six (13.6%) cases while divergence was found in 22 (50%) cases. In rest 16 (36.4%) cases, number of veins leaving the nidus was same as number of veins reaching the sinus. Venous stenosis was noted in 11 (25%) cases and sinus stenosis/ occlusion in 9 (15.9%) cases. Venous ectasia was present in 23 (52.3%) cases, while venous varix was present in 5 (11.4%) cases. In 15

(34.1%) cases of high flow BAVMs we could see venous reflux in cortical veins.

Based on the classification according to the Spetzler–Martin scale, there were 5 (11.4%) Grade I AVMs, 15 (34.1%) Grade II, 12 (27.3%) Grade III, 9 (20.5%) Grade IV and 3 (6.8%) Grade V.

Table 5: Spetzler-Martin grade of BAVMs

Spetzler-Martin grade	No: of patients	Percentage (%)
Grade I	5	11.4
Grade II	15	34.1
Grade III	12	27.3
Grade IV	9	20.5
Grade V	3	6.8

EMBOLIZATION

Total 44 BAVMs were embolized in 74 sessions (1.68 sessions per patient, range 1-4 per patient). Twenty-four (54.5%) patients underwent one procedure; 13 (29.5%), two procedures; 4 (9.1%), three procedures and 3 (6.8%), four embolization procedures. Mean duration of the treatment is 7.55 months (range 0 to 84 months).

Total 150 feeders were embolized in 74 sessions (2.03 feeders per session and 3.41 feeders per patient), out of which 78 were embolized with

Onyx and 72 with other embolic materials including glue (N- butyl cyanoacrylate, NBCA), PVA (poly vinyl alcohol) particles, alcohol and coils (GDC or fiber coils). Most of the arterial pedicles in which other embolic materials were used were embolized before availability of Onyx in our institute, i.e. before February 2006. After its availibility, Onyx was the primary agent used for embolization of nidus. Onyx, which was used in all cases, was Onyx 18 with lowest viscosity. In cases of intranidal arterio-venous fistula we still used glue (NBCA) and in cases of proximal and distal arterial aneurysms we coil them with GDC coils.

Total 128.25 ml Onyx was injected over 3716 minutes. On average 1.64 ml of Onyx (range 0.2 to 7.5 ml) was injected in each feeder over average 47.64 minutes (range 15 to 120 minutes).

Of the 78 feeders embolized with Onyx, 61 were embolized using Ultraflow HPC microcatheter while 17 were embolized using Marathon microcatheter. Transcend 0.010" microguidewire was used with Ultraflow HPC microcatheter and Mirage (0.008") microguidewire was used with Marathon microcatheter in all cases.

EMBOLIZATION RESULTS

The treatment has been completed in 23 (52.3%) of the 44 patients. The remaining 21 (47.7%) are still undergoing the course of endovascular

treatment with additional embolization sessions to be performed or are waiting for stereotactic radiotherapy.

Percentage of obliteration achieved on immediate postembolization check angiogram is as follows:

Table 6: Percentage of obliteration of BAVM on immediate postembolization check angiogram

Percentage of embolization	No: of patients	Percentage (%)
Total (100%)	4	9.1
Near-total (> 90%)	10	22.7
Sub-total (>50%)	17	38.6
Partial (< or = 50%)	13	29.5
Total	44	100

Clinical follow-up was available in 39 (88.64%) patients, while imaging (MRI with MRA or DSA) was available in 27 (61.36%) patients.

Total 61.08 patient-years of clinical follow-up were obtained with mean 1.39 yrs per patient (range 0- 3.33 years or 0-40 months). mRS score on presentation and at last clinical follow-up is as follows-

Table 7: mRS score at presentation and at last clinical follow-up

mRS score	At presentation	At last clinical follow-up
0	0	23 (52.27%)
1	22 (50%)	14 (34.1%)
2	10 (22.7%)	5 (11.4%)
3	5 (11.4%)	0
4	3 (6.8%)	2 (4.5%)
5	4 (9.1%)	0
6	0	0
Mean mRS	2.02	0.75

mRS score of patients was found to be improved in 35 (79.5%) patients, remained same in 7 (15.9%) patients and worsened in 2 (4.5%) patients. Out of the last two patients who worsened one patient with left frontal cortico-ventricular compact nidus BAVM developed perprocedure haemorrhage, which required surgical evacuation of hematoma. Patient developed dysarthria and weakness and sensory loss on left half of the body that gradually improved on physiotherapy. At one-year follow up her dysarthria, weakness and sensations have partially improved. Other patient with diffuse left frontal cortico-ventricular BAVM developed weakness in right upper limb and face postembolization, which was attributed to ischemia, confirmed on post-procedure MRI showing acute infarct in left precentral

Table 7: mRS score at presentation and at last clinical follow-up

mRS score	At presentation	At last clinical follow-up
0	0	23 (52.27%)
1	22 (50%)	14 (34.1%)
2	10 (22.7%)	5 (11.4%)
3	5 (11.4%)	0
4	3 (6.8%)	2 (4.5%)
5	4 (9.1%)	0
6	0	0
Mean mRS	2.02	0.75

mRS score of patients was found to be improved in 35 (79.5%) patients, remained same in 7 (15.9%) patients and worsened in 2 (4.5%) patients. Out of the last two patients who worsened one patient with left frontal cortico-ventricular compact nidus BAVM developed perprocedure haemorrhage, which required surgical evacuation of hematoma. Patient developed dysarthria and weakness and sensory loss on left half of the body that gradually improved on physiotherapy. At one-year follow up her dysarthria, weakness and sensations have partially improved. Other patient with diffuse left frontal cortico-ventricular BAVM developed weakness in right upper limb and face postembolization, which was attributed to ischemia, confirmed on post-procedure MRI showing acute infarct in left precentral

gyrus. Patient was managed conservatively, and with physiotherapy her weakness gradually improved. However at two years and five months follow up she still has the residual weakness.

Total imaging follow up of 0.6 yrs per patient (range 0-2.42 yrs or 0-29 months) was obtained. Out of the 27 patients with imaging follow up, MRI with contrast-enhanced MRA was done in 15 patients and DSA was done in 12 patients. Percentage of obliteration on last imaging available was as follows-

Table 8: Percentage of obliteration on last check angiogram available (including all patients)

Percentage of embolization	No: of patients	Percentage (%)
Total (100%)	5	11.4
Near-total (> 90%)	13	29.5
Sub-total (>50%)	13	29.5
Partial (< or = 50%)	13	29.5
Total	44	100

Out of these 44 patients, only 23 patients have completed the treatment, while others are still under treatment waiting for additional sessions for embolization or waiting for stereotactic radiotherapy.

Table 9: Percentage of obliteration on last check angiogram available in 23 patients with completed treatment

Percentage of embolization	No: of patients	Percentage (%)
Total (100%)	5	21.7
Near-total (> 90%)	13	56.5
Sub-total (>50%)	4	17.4
Partial (< or = 50%)	1	4.4
Total	23	100

In five patients (21.7%), BAVM was cured by embolization alone, while in rest of the patients (18 patients, 78.3%) the residual nidus was treated with stereotactic radiotherapy. From immediate post-embolization angiogram to last angiogram available, the percentage of obliteration of nidus was same in 34 (77.3%) cases; while the size of residual nidus decreased in 7 (15.9%) patients, which could be attributed to regression of perinidal proliferative angiopathy. In three (6.8%) patients of BAVM, size of the nidus increased on follow-up angiogram, which could have occurred due to recruitment of new feeders to the residual BAVM.

Out of thirteen arterial aneurysms, twelve were embolized; while in one patient with right midbrain compact nidus BAVM, subtotal obliteration of BAVM was achieved and proximal arterial aneurysm on right P1 was left

untreated. Follow-up angiogram at one month showed persistence of the aneurysm.

COMPLICATIONS

Following table shows the procedure related complications that occurred in the patients with BAVMs embolized with Onyx.

Table 10: Complications

	Number of patients	Percentage (%)
Deficits	9	20.45
Temporary deficit	5	11.37
Permanent deficit	4	9.1
Death	0	0
Haemorrhage	Clinically significant 6	13.64
	Clinically not significant 2	4.55
Thromboembolic	Clinically significant 3	6.82
	Clinically not significant 2	4.55
Technical complications	3	6.82
Microguidewire perforation	2	4.55
Catheter breakage	1	2.27

Of eight patients with haemorrhage [8 of 44 patients (18.18%), 8 of 74 procedures (10.81%)], five patients bled during the procedure, two patients on same day after the procedure and one on first post-procedure day. Haemorrhage was clinically significant in six cases (3 with temporary and 3 with permanent deficits) while in two cases it was not associated with any

clinical sequele. Four patients had undergone surgical evacuation of the hematoma. Two of these developed permanent deficits while other two had temporary deficits that improved on follow-up. Two patients with haemorrhage were managed conservatively. One of them had small hematoma on post-procedure day one and patient did not develop any deficits. Other patient developed right frontal lobe bleed with subarachnoid haemorrhage during procedure without significant mass effect. This patient developed left upper limb and face weakness with left upper limb numbness that improved partially at eighteen months follow-up. In one patient extravasation of contrast was noted on check angiogram after pulling out the microcatheter. The bleeding artery was immediately embolized with 20% glue (NBCA). Post-procedure CT scan showed subarachnoid haemorrhage and hydrocephalus. Extra-ventricular drainage tube was kept and patient was managed conservatively. Clinically, patient developed paraesthesia on left face, which got completely recovered at one-year follow-up. In one patient small contrast leak was noted on check angiogram after the placement of microcatheter. The bleeding artery was immediately embolized with 33% glue (NBCA). Patient didn't develop any deficit.

Thromboembolic complications occurred in five patients [5 of 44 patients (11.37%), 5 of 74 procedures (6.76%)], with clinically significant infarcts developing in three patients (2 with temporary and one with

permanent deficits). One of these patients developed narrowing of left middle cerebral artery M1 segment during the procedure. Total 4,00,000 IU of urokinase was given. Post-thrombolysis check angiogram showed good opening of M1 segment. Post-procedure patient did not have any deficit. One patient had developed infarct in left precentral gyrus. Clinically patient had right upper limb and face weakness. Patient was managed conservatively and she gradually improved on physiotherapy, however she still had residual weakness at 29 months follow-up. Similarly one other patient developed weakness in right upper and lower limb after the procedure, which completely improved at 18 months follow-up. In one patient, during the procedure, the central branch of right middle cerebral artery got thrombosed. 1,80,000 IU of urokinase was given to open up the middle cerebral artery branch, but it did not open up. Check angiogram showed good filling of occluded branch territory via pial collaterals. So the procedure was abandoned. Post-procedure patient did not develop any deficits. One patient with right fronto-parietal cortico-ventricular compact nidus BAVM developed perinidal infarct and mild weakness on left side of the body that improved completely on follow-up of 16 months.

One patient had seizure on 7th post-procedure day. CT scan was done and it showed cortical vein thrombosis with brain edema. Patient was managed

conservatively with anti-epileptics and anti-edema measures. At twenty-three month follow-up patient had no complaints.

Temporary deficits were noted in 5 (11.37%) patients, which improved on follow-up. Morbidity resulting in permanent deficit occurred in four (9.1%) cases: one case of dysarthria, one case of dysarthria with left hemiparesis and mild hemisensory loss, one case of right upper limb and facial weakness and one case of left upper limb weakness. No procedure related deaths were noted in our series.

Technical complications in form of microguidewire perforation occurred in 2 (4.55%) cases. In one patient rupture site was immediately occluded with glue (NBCA) without any clinical sequele. Another patient had to undergo surgical evacuation of hematoma. She developed left hemiparesis, which improved completely on one-year follow-up. Catheter breakage occurred in one patient with right temporal cortico-subcortical compact nidus BAVM. Marathon microcatheter got stuck in middle temporal branch of right middle cerebral artery, which was very tortuous, after 25 minutes of injection and about 2 cm proximal reflux. While pulling the catheter it got broken with proximal end lying in right common carotid artery. The proximal end of microcatheter was pushed in external carotid artery. Patient was put on antiplatelets without any thromboembolic complications.

We noted catheter gluing in seven cases following Onyx injection. In these cases catheter gluing was associated with prolonged injection times (80 mins in 2, 90 mins in 2, 100 mins in 1, 110 mins in 1 and 120 mins in 1) with reflux of about 1.5 cm. In all these instances we intentionally continued injection for prolong periods to achieve more complete nidus obliteration. In all these cases catheter was cut at skin surface at the puncture site and patients were put on antiplatelet therapy without any thromboembolic complications.

Figures

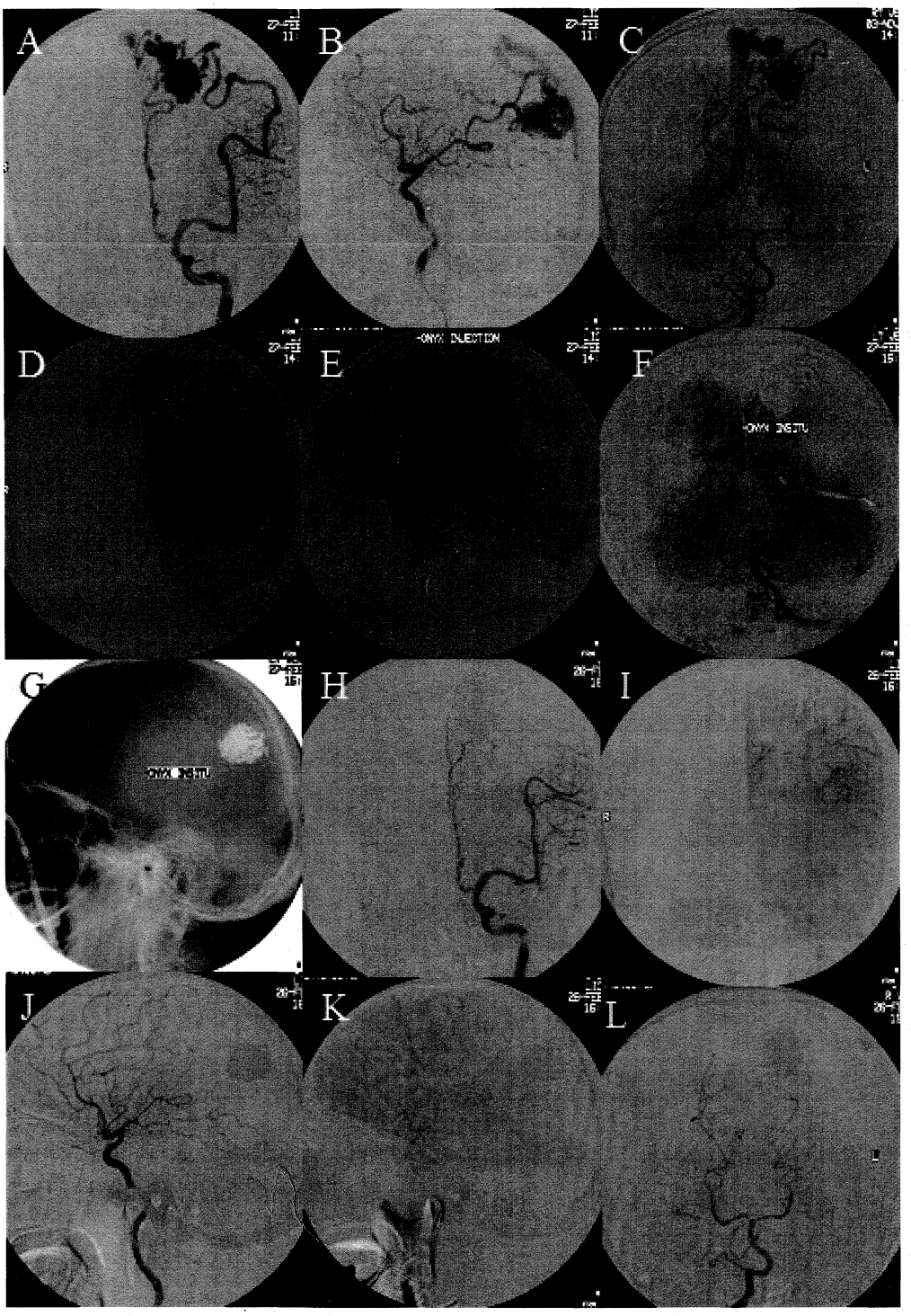


Figure 1. A 44-year old male patient presented with hemorrhage. Left internal carotid artery and left vertebral artery angiogram (**A-C**) showed left parietal cortico-subcortical compact nidus BAVM, supplied by pericallosal branch of left anterior cerebral artery, angular branch of left middle cerebral artery and parieto-occipital branch of left posterior cerebral artery. Three feeders were embolized with Onyx**.** Immediate post embolization angiogram (**D-F**) showed complete obliteration of the nidus. Image **G** is showing Onyx cast in situ. Check angiogram (**H-L**) at one-year follow-up confirmed the complete cure.

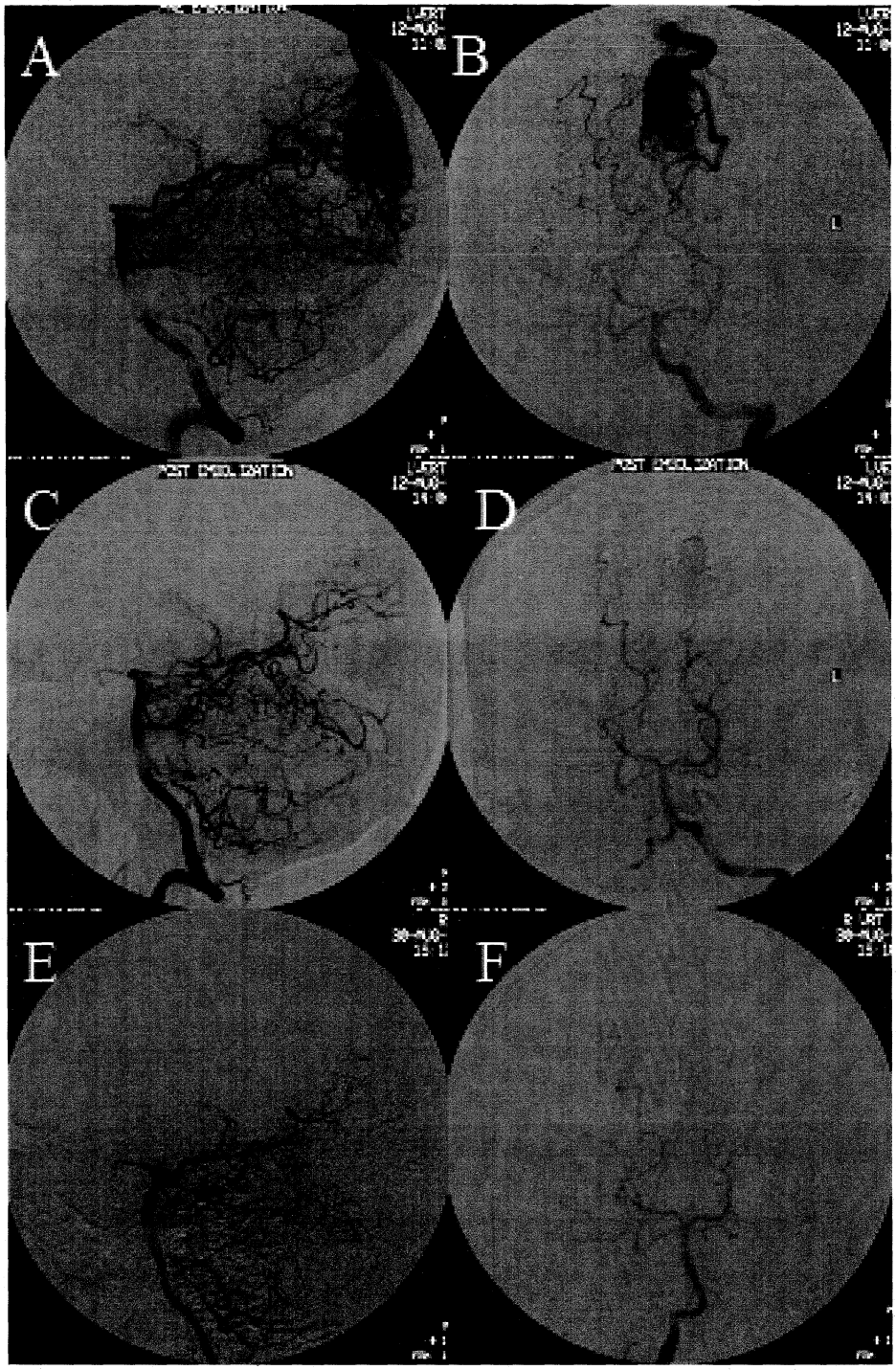


Figure 2. A 26-year old male patient presented with disabling headache. Left vertebral artery injection lateral (**A**) and Towne's view (**B**) showed left occipital cortico-subcortical compact nidus BAVM, supplied by parieto-occipital branch of left posterior cerebral artery. This feeder was embolized with Onyx. Immediate post embolization check angiogram (**C,D**) showed complete obliteration of the nidus, which was confirmed on one-year follow-up check angiogram (**E,F**).

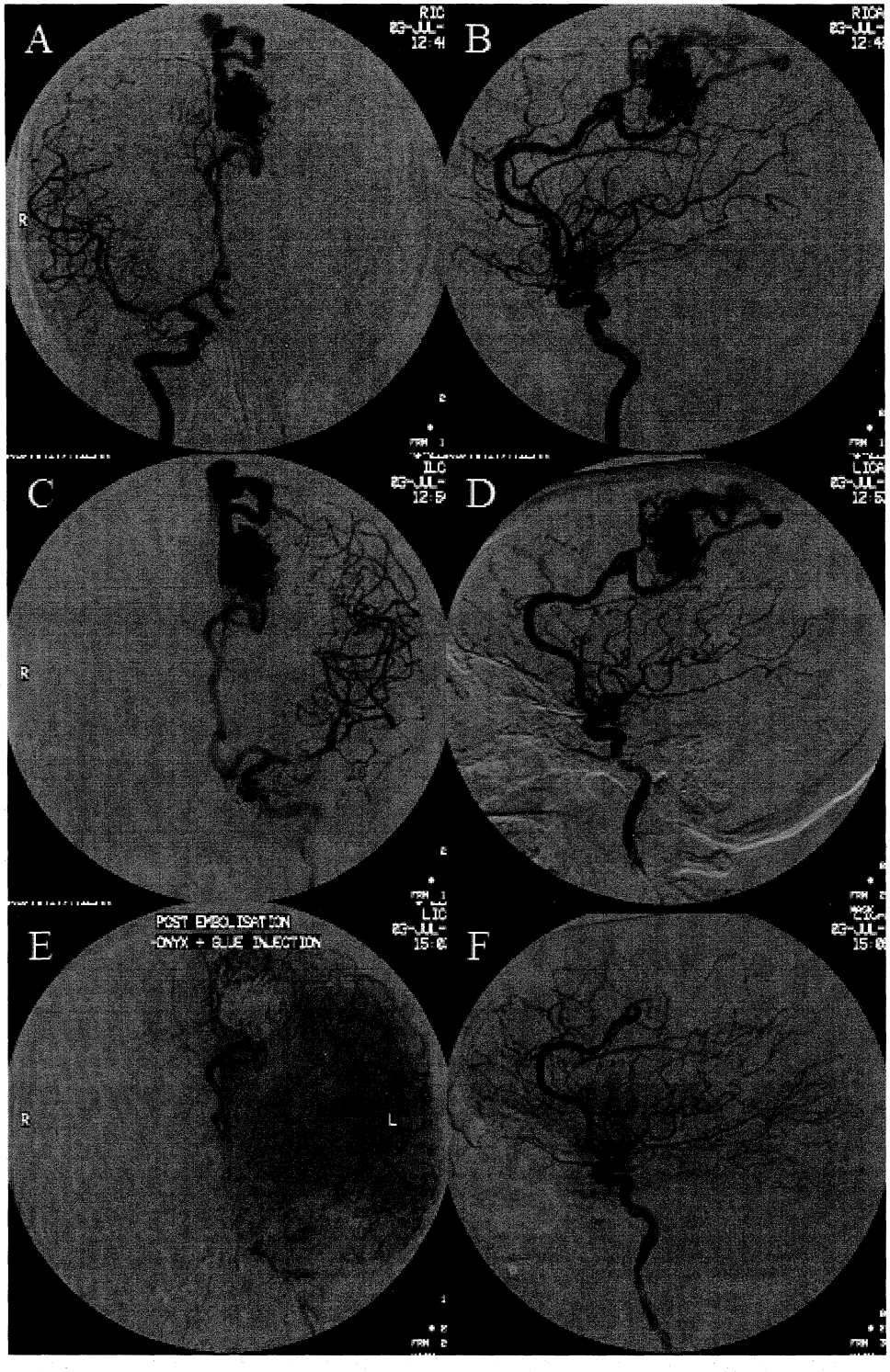


Figure 3. A 29-year old female patient presented with history of seizures. Right (**A,B**) and left (**C,D**) internal carotid artery antero-posterior and lateral views showed left frontal cortico-subcortical compact nidus AVM, supplied posterior internal frontal and calloso-marginal branches of left anterior cerebral artery. Two feeders were embolized, one with Onyx and other with glue (Histocryl). Immediate post embolization left internal carotid artery injection (**E,F**) showed complete obliteration of the nidus.

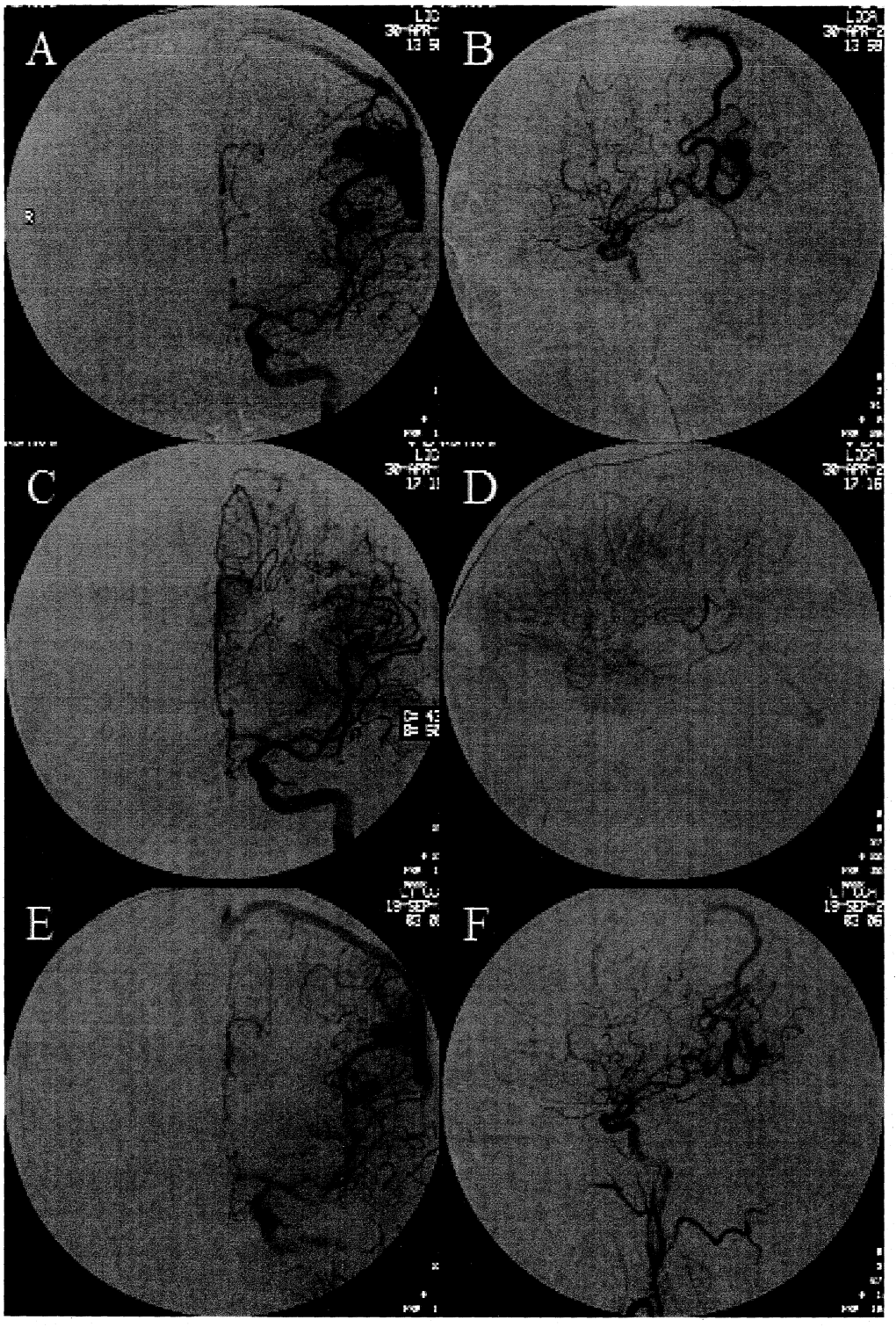


Figure 4. A 26-year old male patient presented with disabling headache. Left internal carotid artery antero-posterior and lateral views (**A,B**) showed left parietal cortico-subcortical compact nidus AVM, supplied by angular branch of left middle cerebral artery. This feeder was embolized with Onyx. Immediate post embolization check angiogram (**C,D**) showed complete obliteration of the nidus. However, check angiogram at 16 months (**E,F**) showed recanalization of the nidus. Patient was planned for second sitting of embolization.

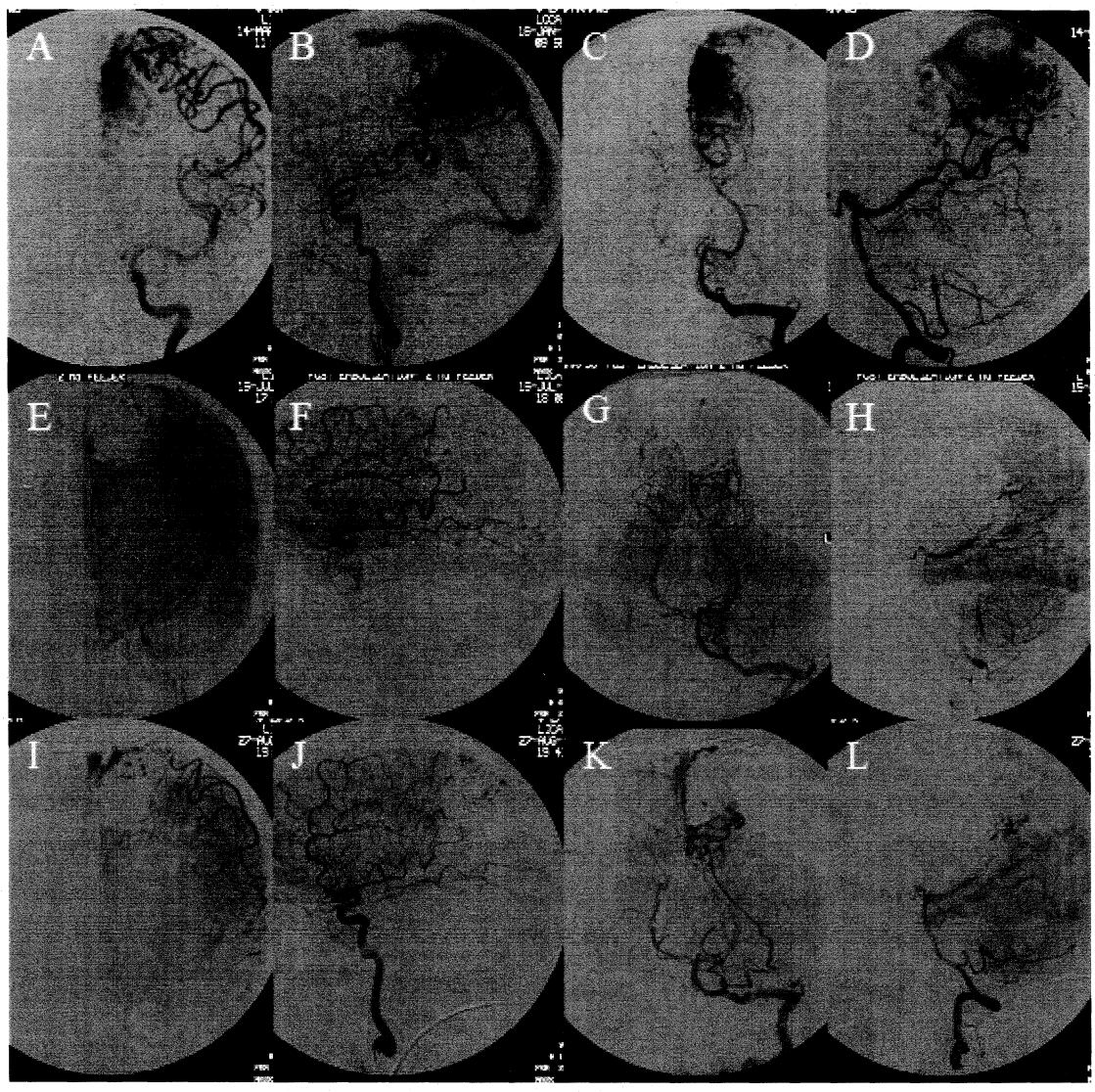


Figure 5. A 12-year old male patient presented with disabling headache. Left internal carotid artery antero-posterior and lateral views (**A,B**) and left vertebral artery Towne's and lateral views (**C,D**) showed left fronto-parietal cortico-subcortical compact nidus AVM, supplied by pericallosal branch of left anterior cerebral artery, angular branch of left middle cerebral artery and parieto-occipital branch of left posterior cerebral artery. Total four feeders were embolized with Onyx in three embolization sessions. Immediate post embolization check angiogram after last session (**E-H**) showed near-complete occlusion of the nidus, which was confirmed at 13 months follow-up angiogram (**I-L**).

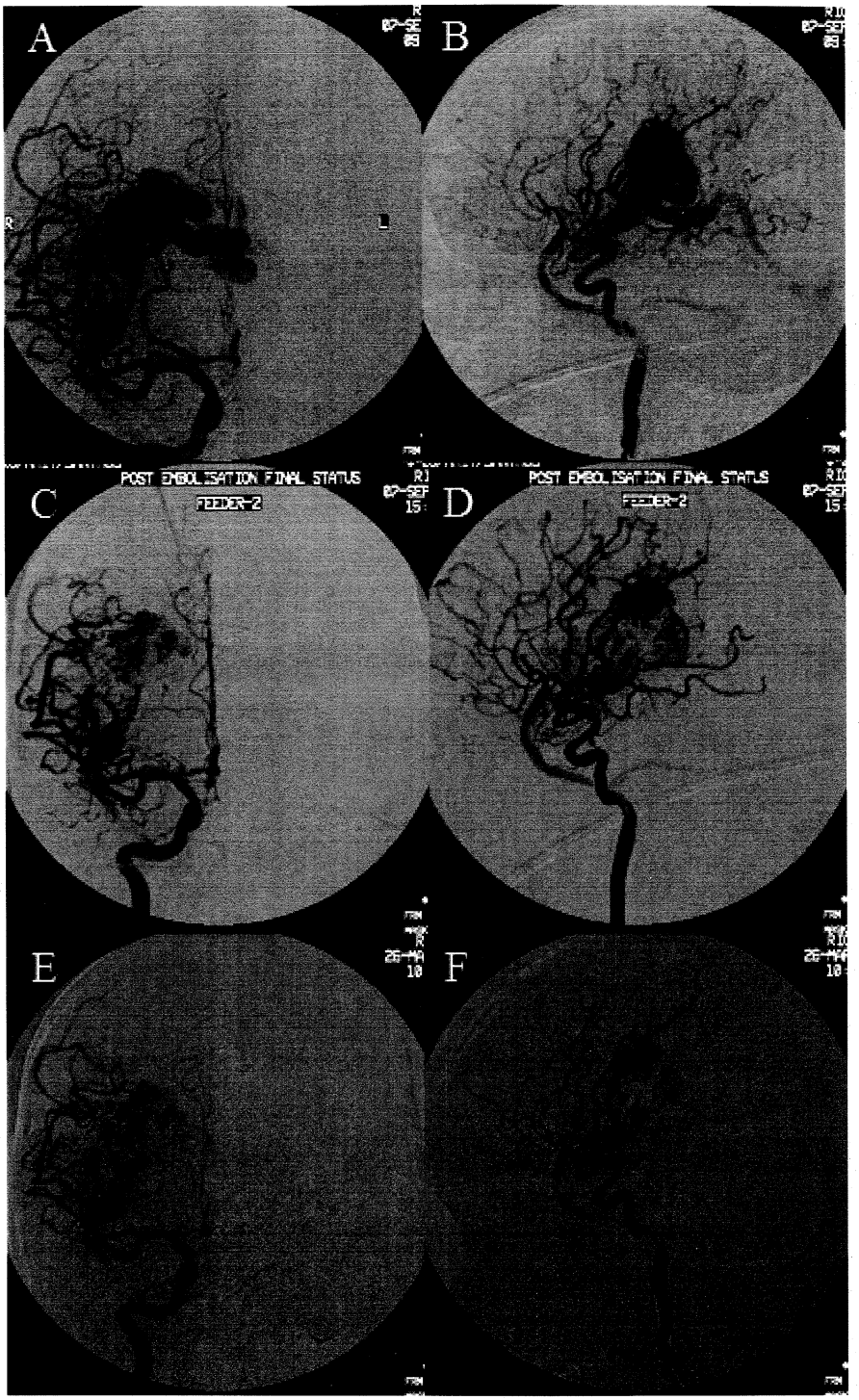


Figure 6. A 17-year old female patient presented with intracranial hemorrhage. Right internal carotid artery antero-posterior view (**A,B**) showed right fronto-parietal cortico-ventricular compact nidus AVM, supplied by insular branches and lenticulo-striate perforators of right middle cerebral artery. Three feeders were embolized in one session. Immediate post embolization (**C,D**) and 6 months follow-up angiogram (**E,F**) showed significant reduction in the size of the nidus.

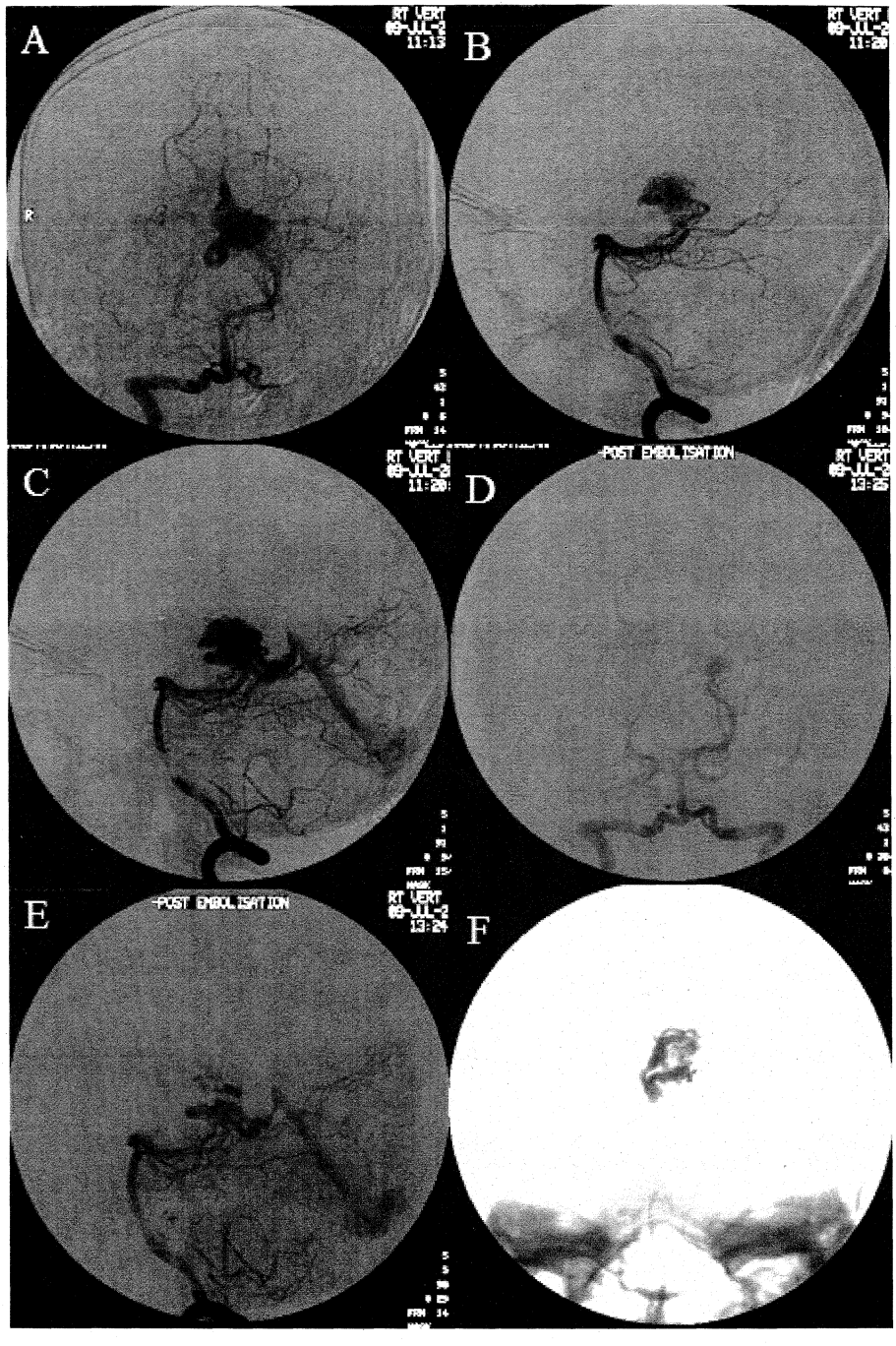


Figure 7. A 23-year old male presented with intracranial bleed. Right vertebral artery injection Towne's (**A**) and lateral (**B,C**) views showed deep-seated left thalamic compact nidus AVM with intra-nidal aneurysm. It was supplied by left thalamo-geniculate perforator and left medial posterior choroidal artery. One feeder was embolized with Onyx. Immediate post embolization check angiogram (**D,E**) showed obliteration of intranidal aneurysm. Image **F** is showing Onyx cast.

Discussion

DISCUSSION

BAVM is the most common intracranial vascular malformation with the prevalence of roughly 0.02-0.11% of general population[6,61,62].

It is the second most common cause of spontaneous intracerebral haemorrhage in an adult[9]. The risk of intracranial haemorrhage in a BAVM has been estimated to be between 2% to 4% yearly[65,70]. In the patient with previous history of haemorrhage, the risk of re-haemorrhage is 6% for first year and then it returns to the baseline level[70]. First haemorrhage is associated with a mortality of 10%, reaching up to 20% for subsequent recurrent haemorrhages[71]. The annual rate of mortality is 1% and that of severe morbidity is 1.7%[65]. In the prospective study by Ondra et al (1990), 85% of the patients who bled, corresponding to 34% of the patient population of the study, either died or suffered severe morbidity during the 24 years of the study[65].

Mean age of presentation of BAVM is 30-40 years[67]. Mean age of the patients in this study was 27.66 yrs (range 7-49yrs). There is no sex predominance noted[67]. We also did not found any significant sex preference [females 20 (45.5%) and males 24 (54.5%)].

Haemorrhages followed by seizures are the most common presenting symptoms[11,56,62]. Other symptoms include headache and focal neurological deficit[78,79]. In our study also haemorrhage was the commonest presenting symptom (36.4%, 16/44 patients), followed by seizures (34.1%, 15/44 patients). Headache (20.4%, 9/44 patients) and focal neurological deficit (9.1%, 4/44 patients) were less common presenting symptoms.

BAVMs are commonly located supratentorially[6]. In our study 3 AVMs were located in infratentorially (6.82%) and remaining 41 supratentorially (93.18%). Of these 41 supratentorial BAVMs, 3 were deep-seated (7.32%), while 38 were hemispheric (92.38%).

Flow in BAVM is very high and is known to induce changes in feeding arteries, termed as high-flow angiopathy. This includes arterial enlargement (most of the patients), arterial stenosis (17%), flow related aneurysms (2.7 to 51.5%) and transfer of watershed[45-48,72]. We also noted high flow angiopathic changes in form of arterial enlargement (in all cases), feeding artery stenosis (9/44, 20.5%), transfer of watershed (10/44, 22.7%) and flow-related feeding arterial aneurysms (13/44, 29.55%). Presence of feeding arterial aneurysm is considered as marker for increased risk for future hemorrhage[49]. However Miesel et al (2000) showed that the patients with feeding arterial aneurysms exhibited the same initial bleeding rate, as did patients without aneurysms[52]. In our study also, we could not find statistically significant differences in the

initial bleeding rate of patients with and without feeding arterial aneurysms (*P* value = 0.732). Five of the twelve patients (41.67%) with feeding arterial aneurysms presented with haemorrhage, while eleven of the thirty-two patients (34.38%) without aneurysms presented with haemorrhage.

Dural supply to BAVMs can occur due to its hemodynamic and angiogenic effects and these can be induced by surgery, embolization or subarachnoid hemorrhage[45]. In our study dural arterial supply was noted in 10 (22.73%) patients. Of these five had undergone embolization previously, one had history of previous surgery, two patients presented with haemorrhage, one with seizure and one with focal neurological deficit.

Intranidal aneurysms/ pseudoaneurysms (arterial or venous) are associated with increased risk of future haemorrhage[52]. All the four patients with intranidal aneurysms in our study presented with hemorrhage.

Deep venous drainage is associated with increased risk of haemorrhage[45,46,59]. In our study, 10 of 26 (38%) patients with deep venous drainage presented with haemorrhage compared to 6 of 18 (33.33%) patients with out deep venous drainage. As described by Valavanis et al (1998) and Berenstein et al (2004) we also noticed high-flow angiopathic changes in draining veins in form of venous ectasias in 23 (52.3%) patients, venous stenosis in 11 (25%), sinus stenosis/ occlusion in 9 (15.9%) and venous varix

in 5 (11.4%) patients[45,46]. Cortical venous reflux was seen in 15 (34.1%) patients.

Based on the classification according to the Spetzler–Martin scale, majority of our BAVMs were of Grade II to Grade IV [5 (11.4%) Grade I, 15 (34.1%) Grade II, 12 (27.3%) Grade III, 9 (20.5%) Grade IV and 3 (6.8%) Grade V] [111].

The main aim of treating BAVMs is to prevent new or recurrent haemorrhage. Other goals include treatment of intractable epilepsy, disabling chronic headaches and focal neurological deficits[3,46].

A basic rule is that a patient should be treated if an improvement over the expected natural history (relevant to that patient because of clinical symptoms, age, angioarchitecture, etc.) will result following treatment. So the treatment associated risk pertinent to the local team (involved in treatment of BAVM) should be considered in comparison with the natural history of AVMs[3,46]. In case of combination treatments, the combined risk of the several treatments should be compared with the natural history. Indications for embolization includes curative embolization, partial (targeted) embolization, partial (palliative) embolization, pre-operative and pre-radiotherapeutical embolization[3,46].

Since the first published description of therapeutic BAVM embolization in 1960, various particulate embolic agents (Silastic spheres, balloons, silk, alcohol, PVA particles) have been used for pre-operative embolization of BAVMs[14-24]. NBCA, a liquid adhesive was approved for use by the United States of Food and Drug administration in 2000. In 1997, Debrun et al reported on the advantages of using NBCA as opposed to particles, for embolizing BAVMs in 54 patients and showed complete occlusion in 5%-10% by embolization alone[144]. Lundquist et al (1996) reported complete occlusion in 13% and Valvalnis and Yasargil (1998) reported anatomic cure in 40% cases with NBCA[46, 148].

Taki et al in 1990 first described the use of Onyx in embolization of BAVMs[30]. But later reports showed toxicity of DMSO solvent, which prevented its widespread use[149,150]. Later Murayama et al and Chaloupka et al demonstrated absence of toxic effect of DMSO in animal experiments, when injected in low dose and at slower rate[151,152]. It was only after Jahan et al, who in 2001 described the injection protocol of DMSO to prevent complications, that Onyx became popular. Onyx gained Food and Drug Administration approval in 2005. Recent studies have established safety and efficacy of Onyx for preoperative and curative embolization of intracranial AVMs[32-44].

This study was done to evaluate the technique and results of endovascular embolization of BAVMs with Onyx and to study the

complications associated with it. Total 44 patients were included in this study, starting from February 2006, when onyx was used for first time in our institution, till August 2009.

Goal of embolization was curative embolization, whenever it was achievable. If that was not possible, we opted for either partial targeted embolization, or pre-operative or pre-radiotherapeutical embolization. In case of partial targeted embolization the aim was to obliterate the weak areas in angioarchitecture like distal arterial or nidal arterial aneurysms or intranidal aneurysms or to decrease venous hypertension by embolizing intranidal arterio-venous fistula.

Onyx is available in four different concentrations, Onyx 18, 20, 34 and 500. Of these Onyx 18 is least viscous and penetrates more distally and is best suited for BAVM nidus embolization. We used Onyx 18 in all our cases. However, because of its low viscosity, this Onyx cannot be used for embolization of intranidal arterio-venous fistula, for which we used glue (NBCA).

Plenty of evidence exists among neurointerventionalists that Onyx possesses superior delivery characteristics and enables increased AVM nidus penetration, potentially resulting in decreased blood loss and less catheter adherence than NBCA.

Onyx appears to offer certain theoretical and experimental advantages over cyanoacrylate.

1. Its slow solidification allows for a more prolonged and controlled injection that enables larger parts of the malformation being occluded with each micro-catheterization[31-44].

2. It also offers long injection times, possible for angiographic control and assessment and continuation of the injection until the desired result is achieved[31-44].

3. The stream of Onyx does not break up during injection; thereby avoiding the formation of small bubbles that may travel out of control, as frequently happens with NBCA. Its behaviour is thus more predictable[31-44].

We performed embolization with Onyx using a technique that could be described as "road-blocking"- the creation of resistance in the direction that the operator does not want the material to advance. When Onyx is injected into a complex multi-channel vascular network like an AVM, it is natural for it to advance in the direction of least resistance. In the beginning of the embolization from a specific pedicle, the material is carried distally by the blood flow. Very quickly, when the blood flow is obstructed by the presence of the Onyx, the direction in which it will advance in this multi-channel network depends solely on the resistance it meets in each channel. When the

resistance to distal movement exceeds that of proximal movement, the Onyx will start flowing back over the micro-catheter. At this point, the operator has to create-by means of repeated, very small volume injections- a dense "plug" that will make the proximal movement of Onyx impossible and oblige the material to move distally once again.

When the material enters an undesired channel, such as a vein or an artery leading away from the AVM (through an anastomosis with a different feeding pedicle), we should stop for 2 minutes and inject small volume again. This is repeated till Onyx start flowing in other desirable direction.

Clinical follow-up was available in 39 (88.64%) patients, while imaging (MRI with contrast-enhanced MRA or DSA) was available in 27 (61.36%) patients. Follow-up imaging with DSA is usually recommended. However, advanced MRI techniques like three-dimensional dynamic time resolution- contrast enhanced MRA technique using combination of parallel imaging technique (ASSET: array spatial sensitivity encoding technique) and time resolved method (TRICKS: time resolved imaging of contrast kinetics) at 1.5Tesla MRI and contrast-enhanced three-dimensional time of flight MRA at 3Tesla MRI have shown promising results comparable to DSA in detection of residual BAVMs[100,155,156]. Total 61.08 patient-years of clinical follow-up were obtained with mean 1.39 yrs per patient (range 0- 3.33 years or 0-40 months).

Total occlusion rate with Onyx as described in literature ranges from 0 to 53.9%[31-44]. In our study, considering all patients, the total (100%) occlusion rate at last imaging follow-up was 11.4% (5/44) and near-total (>90%) occlusion rate was 29.5% (13/44). However, considering 23 patients in whom treatment was completed, the total occlusion rate with embolization alone was 21.7% (5/23). In rest of the patients the residual BAVM was treated with stereotactic radiotherapy.

Clinical outcome was excellent in 23 (52.27%) patients with mRS score 0. On the last clinical follow-up available, mRS score was improved in 35 (79.5%) patients, remained same in 7 (15.9%) and worsened in 2 (4.5%) patients.

Technical complications:

There are some technical complications associated with the use of Onyx. This includes:

1. One of the advantages of Onyx, the high radio-opacity, can also be a disadvantage in cases of large AVMs that have already been treated with the injection of large amounts of the material[43]. With the Onyx cast over-projecting on the remaining nidus, it is very difficult and sometimes impossible to visualize the course of the material one is injecting. This can result in the unexpected entry of Onyx in the venous part of the

malformation with possible catastrophic results. Experience has taught us that when we inject a large amount of Onyx and do not observe any significant changes in the appearance of the cast, the material is usually filling a large volume vein and the injection should be stopped immediately.

2. Another disadvantage of Onyx is its poor visualization during reflux in very small vessels, as reported by van Rooij et al[38].

3. Good visual control of the reflux is mandatory to prevent occlusion of a normal territory and to avoid trapping of the microcatheter.

4. In contrast to NBCA, Onyx is a nonadhesive liquid. This basic characteristic eliminates the risk of gluing the catheter to the vessel wall and therefore allows a longer injection time and a wider range of different injection rates. However, despite this advantage, a microcatheter can be trapped within the feeding pedicle during Onyx injection, particularly during long injection, when too much reflux occurs or when the feeding pedicle represents a very distal and tortuous loop[33-44]. Catheter gluing occurred eight times in seven patients [8 of total 78 (10.26%) microcatheters used]. In one patient it was due to too much tortuous feeding artery with increased reflux of Onyx. Catheter got broken while pulling, with proximal end lying in right common carotid artery, which

was later pushed in to distal external carotid artery. In seven other instances it was due to long injection times, which was done intentionally to achieve more complete obliteration of the nidus. All patients with catheter gluing were placed under antiplatelets and none of them developed any thromboembolic complications due to microcatheter.

Other technical complications include microguidewire perforation, which was reported in five cases by Mounayar et al and in one case by Katsaridis et al. We noticed microguidewire perforation in 2 (4.55%) cases. Rupture site was immediately occluded with glue in one patient without any clinical complications. In another case surgical evacuation of hematoma was required, after which patient developed left hemiparesis, which recovered fully on one-year follow-up.

Clinically significant complications:

Intra-operative hemorrhage can occur as a result of vessel perforation during microcatheter placement in fragile AVM vessels, especially when the wire-guided technique is employed for catheterization[38-40,43]. We encountered this complication in two cases; one case was embolized with glue, while other had to undergo surgical evacuation of hematoma.

The major clinically significant complication of AVM embolization is acute postembolization hemorrhage (APEH), the most neurologically

devastating complication of embolization[157,158]. Kvam et al (1980) were the first to report on postembolization hemorrhage[159]. Picard et al (2001) reviewed the literature and presented the largest series on APEH. Rate of APEH using intranidal injection technique was 1% per embolization and 3% per patient [158]. In the patients with BAVM embolized with Onyx, the rate of APEH described in large series ranges from 5.9 to 7.5% per patient[39,40,43,44]. In our study we had per- and peri-procedural clinically significant haemorrhage in six patients (6/44, 13.66% per patient; 6/74, 8.11% per procedure), four patients bled during the procedure, one patients on same day after the procedure and one on first post-procedure day.

Early APEH is thought to be caused by hemodynamic changes after embolization, mainly by alterations in feeder pressures[157,160,161]. Factors that have been found to predispose APEH include significant venous embolization, certain angio-architectural features, persistent venous stagnation within the nidus, and progressive venous thrombosis[43,157,160,161]. We had three cases of early APEH; one patient was managed conservatively with no clinical deficit; two had to undergo surgical evaculation of hematoma, following which one developed temporary deficit and other permanent deficit.

Occlusion of the draining venous outlet during embolization of AVMs can be devastating. Hademenos et al (1996) employed a bio-mathematical AVM model using electrical network analysis and noted that impairment of

total drainage of AVM induced a rapid redistribution of blood into the weak plexiform vessels of the residues of the nidus, causing a hemodynamic overload and an increased of rupture[162].

However, embolization of a draining vein does not always lead to complications. The risk of bleeding after the drainage system is impaired depended on the dynamic importance of the occluded draining vein and flow changes through the nidus[163]. In AVM associated with a marked venous outflow obstruction, the initial embolization is aimed at diminishing the flow through the nidus compartment draining through the stenosed or ectatic veins. In the unwanted instance of venous outflow occlusion during embolization, the patient should be sedated and monitored carefully, and blood pressure maintained below 90 mm Hg for 48-72 hours[164]. If the total drainage is severely impaired, emergency surgical excision of the residues of the nidus may be a wise choice.

The etiology of late or delayed hemorrhage has been postulated to include venous outflow obstruction or hemodynamic changes attributable to normal perfusion pressure breakthrough, a rare phenomenon in which chronic hypoperfusion of normal brain parenchyma adjacent to an BAVM results in a disruption of vascular autoregulation[157,158,164-166]. We did not encounter any case of delayed hemorrhage.

In regard to late or delayed APEH, Purdy et al postulated that delayed vein occlusion might occur because of sluggish flow rather than by direct occlusion of the vein by embolic material[157]. Although venous occlusion may be a goal when attempting intranidal embolization to achieve complete occlusion, continued inflow into the malformation with impaired outflow increase the risk for rupture and haemorrhage. Venous congestion in the adjacent brain might progress by delayed thrombosis in the draining vein, leading ultimately to venous bleeding. One of our patient developed seizure on 7th post-procedure day. CT scan was done and it showed cortical vein thrombosis with brain edema. Patient was managed conservatively with anti-epileptics and anti-edema measures. At twenty-three month follow-up patient had no complaints.

Normal perfusion pressure breakthrough is believed to occur in patients with low-resistance, high-flow giant AVMs with multiple large arterial feeders or in AVMs associated with high-flow arteriovenous fistulas because these malformations exhibit greater shunts and thus a greater "vascular steal" effect on adjacent cortex[167]. Normal perfusion pressure breakthrough-associated bleeding can be minimized through blood pressure control in the immediate postoperative period and staging the embolization of the large AVM[159,160]. In our study, during embolization of BAVM, we maintained the systolic arterial

pressure at 90-100mm Hg intraprocedure and during the first 24 hours after embolization.

Some of our embolizations were staged. This was done in cases of large BAVMs or in some cases to allow a small feeder to enlarge in order to facilitate future catheterisation[3].

About 2.7 to 51.5% BAVMs are associated with feeding arterial aneurysms[47,48]. Piotin et al (2001), who considered that proximal aneurysms with BAVMs have a greater propensity to rupture when compare with aneurysms in patients without BAVM, suggested that proximal AVM-associated aneurysms should be treated first, especially when the aneurysm has been identified as a source of hemorrhage[168]. Gao et al (1997), Bradac et al (2001) and Li et al (2005) proposed that intranidal or feeding artery aneurysms are the fragile part in BAVMs and the increasing flow and pressure in the residual nidus and feeding artery after partial embolization raise the risk of this fragile structure rupture, so the aneurysm should be embolized first[163,169,170].

On the contrary, Redekop et al (1998) and Meisel et al (2000) observed the shrinkage of arterial aneurysms after endovascular treatment of BAVM and concluded that the aneurysms should not be the primary targets of embolization compared BAVM[12,55]. They notice regression of proximal and distal flow related aneurysms following complete or more than 50%

obliteration of AVM nisus by endovascular means. They noticed that more distal is the aneurysm, higher is the probability of subsequent regression. Berenstein et al (2004) proposed that feeding arterial aneurysms should be treated only if it is identified as a cause of bleed[3]. Otherwise BAVM should be treated primarily and patient should be followed up for 6-12 months, if no regression is seen on follow up angiography active treatment of aneurysm should be considered[3].

We had three patients with proximal arterial aneurysms, one of which (Acom aneurysm) was coiled, while other two (right posterior inferior cerebral artery and posterior cerebral artery origin aneurysms) are followed-up. Three patients with distal arterial aneurysms and seven with nidal arterial aneurysms were embolized.

Ischemic complications mainly occur due to nontarget occlusion, however it may also occur from catheter-induced thrombo-embolic phenomenon[171]. Wedge positioning of the microcatheter at or within the nidus of the BAVM may help to prevent non-targeted embolization[115]. If wedge positioning is not possible, only when no normal parenchymal vessels are opacified with the test injection and the BAVM is located in a noneloquent area or functional testing is negative, can embolization proceed. If en passage feeding artery is due to be embolized, the tip of the microcatheter should be

wedged in the feeder at least 5mm distal to the branch point with the vessel of passage. These measures can minimize the risk of non-target occlusion [115,171].

We had three patients with clinically significant ischemic complications. One patient had developed infarct in left precentral gyrus leading to right upper limb and face weakness. Patient gradually improved on physiotherapy; however she still had residual weakness at 29 months follow-up. One other patient developed weakness in right upper and lower limb after the procedure, which completely improved at 18 months follow-up. One patient developed perinidal infarct and mild weakness on left side of the body that improved completely on 16 months follow-up.

Systemic heparinization and continuous flush of the whole coaxial system with heparinized saline can minimize the risk of catheter induced thrombo-embolic complication. We used systemic heparinization with nimodipine (3mg in 1 litre of saline) in all our patients. We had two patients with thrombo-embolic complication without any clinical deficit. One of these patient developed narrowing of left middle cerebral artery M1 segment during the procedure. After giving 4,00,000 IU of urokinase good opening of M1 segment was noted on check angiogram. Post-procedure patient did not have any deficit. In one other patient, the central branch of right middle cerebral artery got thrombosed during the procedure. 1,80,000 IU of urokinase was given to open up the middle cerebral artery branch, but it did not open up.

Check angiogram showed good filling of occluded branch territory via pial collaterals. So the procedure was abandoned. Post-procedure patient did not develop any deficits.

In our study, we had five (11.37%) patients with temporary deficits and four (9.1%) patients with permanent deficits (total morbidity 9/44, 20.45%). Van Rooij et al (2007) reported cases of immediate post-operative neurological deficits that were unrelated to hemorrhage[38]. Instead all were attributable to onyx reflux and occlusion of a branch supplying the normal brain. Mounayer et al (2007) reported transient deficits in 3% and permanent deficit in 9%, while Katsaridis et al (2008) reported temporary deficits in 6.9% and permanent deficits in 5.9%[40,43].

Procedure related mortality rate ranges from 0 to 3.2%[31-44]. We did not encountered any procedure related death (mortality 0%).

Toxicity of DMSO is well reported in literature. Chaloupka et al (1994) and Sampey et al (1996) described angiotoxic effects of rapid injection of DMSO in animal experiments[149,150]. Later Murayama et al (1998) and Chaloupka et al (1999) showed that when DMSO is injected in low dose and at slower rate, it does not cause angiotoxicity[151,152]. Jahan et al described the injection protocol in a series of 23 patients with total 129 pedicles treated. This article emphasized the critical need for slow and controlled injection of

solvent DMSO[31]. Junior et at (2008) had described neurotoxicity associated with DMSO preserved haemopoietic progenitor cell infusion. We injected DMSO at a recommended slow, steady rate of 0.16 mL/min (0.25 mL/90 sec) without exceeding 0.3 mL/min injection rate. No complications related to DMSO were noted in our study.

One of the most important properties of embolization materials is stability[173]. Although cyanoacrylates have shown good stability, there is evidence supporting the recanalization of BAVMs that are embolized with cyanoacrylates[173-176]. To date, Onyx seems quite stable because recanalization was not seen either in experimental studies up to 6 months after the procedure[151] or in the histological and radiological images presented by Jahan et al[31] who performed surgery as late as 14 days after embolization. As Higashida et al (2001) pointed out, however recanalization may appear later, and this factor is very important in cases of BAVMs treated with embolization followed by radiotherapy, because recanalization may be responsible for the failure of radiotherapeutical treatment[177]. Perez-Higueras et al reported 2 cases of reperfusion among 10 completely embolized AVMs after 2 and 4 years, respectively[37]. More recently, Weber et al reported 2 early angiographic recurrences after complete obliteration of 19 AVMs that were evident at 3-months' follow-up[39].We had two patients in which complete obliteration of nidus was achieved on immediate post-embolization check angiogram, while

follow-up angiogram showed recanalization with filling of the nidus. This can occur if the embolic material is not uniformly distributed in nidus and there are areas of thrombosis in between, which can recanalize later on.

According to Akin et al, there is an advantage for Onyx in intraoperative handling because of its physical characteristics after precipitation[178]. Onyx is a soft, sponge-like mass that is easy to handle during surgery. The embolized vessels are completely filled by embolic agent and are less fragile because of the lower inflammatory reaction and the absence of polymerization heat compared with NBCA embolized BAVMs. Akin et al found less intraoperative blood loss and a shorter duration of surgical procedures for onyx compared with NBCA in an animal model[178].

Table 11: Comparison of previously reported series of onyx embolization of BAVMs with our study:

Series (Ref. no.)	Patients	Angiographic cure, no (%)	Mortality, No. (%)	Permanent neurological deficit, no. (%)
Jahan et al., 2001[31]	23	0	0	9(4%)
Hamada et al., 2002[32]	57	0	0	3(5.3%)
Florio et al, 2003[33]	10	2(20%)	0	1(10%)
Song et al.,2004[34]	3	0	0	1(33.3%)
He et al.,2005[35]	22	3(13.6%)	0	0
Pierot et al., 2005[36]	48	2(4.1%)	1(2%)	5(10%)
Perez-Higueras et al., 2005[37]	45	10(22.2%)	1(2%)	6(15.5%)
Van Rooij et al., 2007[38]	44	7(16%)	1(2.3%)	2(4.6%)
Weber W et al, 2007[39]	93	19(20%)	0	9(9%)
Mounayer et al, 2007[40]	94	26(49%)	3(3.2%)	5(8.5%)
Natarajan SK et al., 2008[41]	28	6(21.4%)	0	1(3.5%)
Velat GJ., et al, 2008[42]	20		1(5%)	3(15%)
Katsaridis et al., 2008[43]	101	28(53.9%)	3(3%)	6(5.9%)
Panagiotopoulos et al., 2009[44]	82	20(24.4%)	2(2.4%)	6(7.3%)
Current study	44	5 (21.7%)	0	4 (9.1%)

As demonstrated by our study, Onyx is a promising embolic agent for endovascular treatment of BAVMs. Because of its nonadhesive nature and lava-like penetration characteristics, it can help to achieve good obliteration rate, with acceptable rate of complications.

Conclusion

CONCLUSION

Following conclusions can be made from this study:

- Embolization with Onyx of brain AVMs is feasible and safe.
- Embolization of BAVM with Onyx results in adequate nidus occlusion with relatively high overall complete obliteration rate (11.4% in this study).
- Onyx, with its non-adherent properties allows a slower and more controllable injection and results in a more effective filling of the BAVM nidus.
- Embolization of BAVM with Onyx is associated with acceptable rates of morbidity and mortality. As with other embolic agents, postembolization hemorrhage is the most important complication.

Bibliography

BIBLIOGRAPHY

1. Challa VR, Moody DM, Brown WR. Vascular malformations in the central nervous system. J Neuropathol Exp Neurol 1995; 54: 609-621.

2. Valavanis A. The role of angiography in the evaluation of cerebral vascular malformations. Neuroimag Clin N Am 1996; 6: 679-704.

3. Berenstein A, Lasjaunias P, terBrugge KG. Goals and objectives in the management of brain arteriovenous malformations. In: surgical neuroangiography. Vol. 2.2, Berlin/Heidelberg: Springer-Verlag: 2004, p. 695-736.

4. Gault J, Sarin H, Awadallah NA, Shenkar R, Awad IA. Pathobiology of human cerebrovascular malformations: basic mechanisms and clinical relevance. Neurosurgery 2004; 55: 1-17.

5. Kaplan HA, Aronson SM, Browder EJ. Vascular malformations of the brain. An anatomical study. J Neurosurg 1961; 18: 630-635.

6. Jellinger K. Vascular malformations of the central nervous system: a morphological overview. Neurosurg Rev 1986; 9: 177-216.

7. Hofmeister C, Stapf C, Hartmann A, Sciacca RR, Mansmann U, terBrugge KG, et al. Demographic, morphological, and clinical characteristics of 1289 patients with brain arteriovenous malformation. Stroke 2000; 31: 1307-1310.

8. Stapf C, Labovitz DL, Sciacca RR, Mast H, Mohr JP, Sacco RL. Incidence of adult brain arteriovenous malformation hemorrahge in prospective population-based stroke survey. Cerebrovasc Dis 2002; 13: 43-46.

9. Yasargil MG. Microneurosurgery, Vol IIIB: AVM of the Brain. Clinical Considerations, General and Specific Operative Techniques, Surgical Results, Nonoperated Cases, Cavernous and Venous Angiomas, Neuroanesthesia. New York, NY: Georg Thieme Verlag; 1988:370-383.

10. Mansmann U, Meisel J, Brock M, Rodesch G, Alvarez H, Lasjaunias P. Factors associated with intracranial hemorrhage in cases of cerebral arteriovenous malformations. Neurosurgery 2000; 46: 272-281.

11. Mast H, Young WL, Koennecke HC, Sciacca RR, Osipov A, Pile-Spellman J, et al. Risk of spontaneous hemorrhage after diagnosis of cerebral arteriovenous malformations. Lancet 1997; 350: 1065-1068.

12. Meisel HJ, Mansmann U, Alvarez H, Rodesch G, Brock M, Lasjaunias P. Cerebral arteriovenous malformations and associated aneurysms: analysis of 305 cases from series of 662 patients. Neurosurgery 2000; 46: 793-802.

13. Stefani MA, Porter PJ, terBrugge KG, Montanara W, Willinsky RA, Fallace MC. Angioarchitectural factors present in brain arteriovenous malformations associated with hemorrhagic presentation. Stroke 2002; 33: 920-924.

14. Luessenhop AJ, Spence WT. Artficial embolization of cerebral arteries: report of use in a case of arteriovenous malformaton. JAMA 1960; 172: 1153-1155.

15. Serbinenko FA. Balloon catheterization and occlusion of major cerebral vessels. J Neurosurg 1974; 41: 125-145.

16. Debrun G, Lacour P, Caron JP, et al. Detachable balloon and calibrated leak balloon techniques in the treatment of cerebral vascular lesions. J Neurosurg 1978; 49: 635-649.

17. Kerber C. Balloon catheter with a calibrated leak: a new system for superselective angiography and occlusive catheter therapy. Radiology 1976; 120: 547-550.

18. Pevsner PH. Micro-balloon catheter for superselective angiography and therapeutic occlusion. AJR Am J Roentgenol 1977; 128: 225-230.

19. Purdy PD, Samson D, Batjer HH, et al. Preoperative embolization of cerebral arteriovenous malformations with polyvinyl alcohol particles: experience in 51 adults. AJNR Am J Neuroradiol 1990; 11: 501-510.

20. Fox AJ, Pelz DM, Lee DH. Arteriovenous malformations of the brain: recent results of endovascular therapy. Radiology 1990; 177: 51-57.

21. Schumacher M, Horton JA. Treatment of cerebral arteriovenous malformations with PVA: results and analysis of complications. Neuroradiology 1991; 33: 101-105.

22. Nakstad PH, Bakke SJ, Hald JK. Embolization of intracranial AVMs and fistulas with PVA and platinum fibre coils. Neuroradiology 1992; 34: 348-351.

23. Devekis JP, Manz HJ, Luessenhop AJ, et al. A clinical and neuropathologic study of silk suture as an embolic agent for brain AVM. AJNR Am J Neuroradiol 1994; 15: 263-271.

24. Yakes WF, Krauth L, Ecklund J, Swengle R, et al. Ethanol endovascular management of brain AVMs: initial results. Neurosurgery 1997; 40: 1145-1154.

25. Debrun G, Vinuela F, Fox A, et al. Embolization of cerebral arteriovenous malformations with bucrylate: experience in 46 cases. J Neurosurg 1982; 56: 615-627.

26. Picard L, Moret J, Lepoire J, et al. Endovascular treatment of intracerebral arteriovenous angiomas. Technique, indications and results. J Neuroradiol 1984; 11: 9-28.

27. Vinuela F, Fox AJ, Debrun G, et al. Preembolization superselective angiography: role in the treatment of brain AVMs with isobuty-2 cyanoacrylate. ANJR Am J Neuroradiol 1984; 5: 765-769.

28. Jafar JJ, Davis AJ, Berenstein A. The effect of embolization with n-butyl cyanoacrylate prior to surgical resection of cerebral arteriovenous malformations. J Neurosurg 1993; 78: 60-69.

29. Wallace RC, Flom RA, Khayata MH, et al. The safety and effectiveness of brain AVM embolization using acrylic and particles: the experiences of a single institution. Neurosurgery 1995; 37: 606-618.

30. Taki W, Kikuchi H, Iwata H, et al. Embolization of arteriovenous malformations using EVAL mixture (a new liquid embolization material). Neuroradiology 1990; 33: 195-196.

31. Jahan R, Murayama Y, Gobin YP, Vinters HV, Vinuela F: Embolization of arteriovenous malformations with Onyx: Clinopathological experiences in 23 patients. Neurosurgery 2001; 48: 984-997.

32. Hamada J, Kai Y, Morioka M et al: A mixture of ethylene vinyl alcohol copolymer and ethanol yielding a nonadhesive liquid embolic agent to treat cerebral arteriovenous malformations: Initial clinical experience. J Neurosurg 2002; 97: 881-888.

33. Florio F, Lauriola W, Nardella M, Trosello MP: Endovascular treatment of intracranial arterio-venous malformations with Onyx embolization: Preliminary experience. Radiol Med (Torino) 2003; 106: 512-520.

34. Song DL, Leng B et al. Clinical experience of 70 cases of cerebral arteriovenous malformations embolization with Onyx, a novel liquid embolic agent. Zhonghua Wai Ke 2004; 45: 223-25.

35. He HW, Jiang CH, Liu HB et al: Endovascular treatment of cerebral arteriovenous malformations with onyx embolization. Chin Med J (Engl) 2005; 118: 2041-2045.

36. Pierot L, Januel AC, Herbreteau D et al. Endovascular treatment of brain AVMs using Onyx : preliminary results of a prospective multicentre study. Interventional Neuroradiology 2005; 11: 159-64.

37. Perez-Higueras, Rossi Lopez et al. Endovascular treatment of cerebral AVM: our experience with Onyx. Interventional Neuroradiology 2005; 11: 141-57.

38. Van Rooij WJ, Sluzewshi M, Beute GN: Brain AVM embolization with onyx. AJNR Am J Neuroradiol 2007; 28: 172-177.

39. Weber W, Kis B, Siekman R, Kuehne D. Endovascular treatment of intracranial avm with Onyx: Technical aspects. AJNR Am J Neuroradiol 2007; 28: 371-377.

40. Mounayer C, Hammami N, Piotin M et al. Nidal embolization of brain AVM using Onyx in 94 patients. AJNR Am J Neuroradiol 2007; 28: 518-523.

41. Natarajan SK, Ghodke B, Born DE et al. Multimodality treatment of brain AVM with microsurgery after embolization with Onyx: Single-Center experience and technical nuances. Neurosurgery 2008; 62: 1213-1226.

42. Velat GJ, Sistrom C, Smullen D et al. Comparison of N-butyl cyanoacrylate and Onyx for the embolization of intracranial arteriovenous malformations: Analysis of fluoroscopy and procedural times. Neurosurgery 63(ons suppl 1) 2008: ONS75-ONS82.

43. Katsaridis V, Papagiannaki C, Aimar E. Curative embolization of cerebral avms with onyx in 101 patients. Neuroradiology 2008; 50: 589-597.

44. Panagiotopoulos V, Gizewski E, Asgari S et al. Embolization of intracranial AVM with EVOH (Onyx). AJNR Am J Neuroradiol 2009; 30: 99-106.

45. Berenstein A, Lasjaunias P, terBrugge KG. Cerebral vascular malformations: Incidence, classification, angioarchitecture, and symptomatology of brain arteriorvenous and venous malformations. In: surgical neuroangiography. Vol. 2.2, Berlin/Heidelberg: Springer-Verlag, 2004; p. 609-694.

46. Valavanis A, Yasargil MG. The endovascular treatment of brain arteriovenous malformations. Adv Tech Stand Neurosurg 1998; 24: 131-214.

47. Paterson JH, McKissock W. A clinical survey of intracranial angiomas with special reference to their mode of progression and surgical treatment: a report of 110 cases. Brain 1956; 79: 233-266.

48. Sakata Y, Higashi K, Aoki H. Simultaneous occurrence of intracranial aneurysms and arteriovenous malformations. Arch Jpn Chir 1998; 37: 242–247.

49. Brown RD, Wiebers DO, Forbes GS. Unruptured intracranial aneurysms and arteriovenous malformations: Frequency of intracranial hemorrhage and relationship of lesions. J Neurosurg 1990; 73: 859-863.

50. Batjer H, Suss RA, Samson D. Intracranial arteriovenous malformations associated with aneurysms. Neurosurgery 1986; 18: 29-35.

51. Lasjuanias P, Piske R, TerBrugge K, et al. Cerebral arteriovenous malformations and associated arterial aneurysms (AA): analysis of 101 cases, with 37 arterial aneurysms in 23 patients. Acta Neurochir (Wien) 1988; 91: 29-36.

52. Meisel HJ, Mansmann U, Alvarez H, et al. Cerebral arteriovenous malformations and associated aneurysms: analysis of 305 cases from a series of 662 patients. Neurosurgery 2000; 46: 793-800.

53. Hayashi S, Arimoto T, Itakura T, Fujii T, Nishiguchi T, Komai N. The association of intracranial aneurysms and arteriovenous malformations in brain. Case report. J Neurosurg 1981; 55: 971-975.

54. Miyasaka K, Wolpert SM, Prager RJ. The association of cerebral aneurysms, infundibula and intracranial arteriovenous malformations. Stroke 1982; 13: 196-203.

55. Redekop G, TerBrugge K, Montanera W, et al. Arterial aneurysms associated with cerebral arteriovenous malformations: Classification, incidence, and risk of hemorrhage. J Neurosurg 1998; 89: 539-546.

56. Perret G, Nishioka H. Report on the cooperative study of intracranial aneurysms and subarachnoid hemorrhage. Section VI. Arteriovenous malformations. An analysis of 545 cases of cranio-cerebral arteriovenous malformations and fistulae reported to the cooperative study. J Neurosurg 1966; 25: 467-490.

57. Newton TH, Cronqvist S. Involvement of dural arteries in intracranial arteriovenous malformations. Radiology 1969; 93: 1071-1078.

58. Russel EJ, Berenstein A. Meningeal collateralization to normal cerebral vessels associated with intracerebral arteriovenous malformations: a functional angiographic study. Radiology 1981; 139: 617-622.

59. Langer D, Lasner T, Hurst R, Flamm E, Zager E, King J. Hypertension, small size, and deep venous drainage are associated with risk of hemorrhagic presentation of cerebral arteriovenous malformations. Neurosurgery 1998; 42: 481-489.

60. Stapf C, Mohr JP. New concepts in adult brain arteriovenous malformations. Curr Opin Neurol 2000; 13: 63-67.

61. Karhunen PJ, Penttila A, Erkinjuntti T. Arteriovenous malformation of the brain: imaging by post-mortem angiography. Rorensic Sci Int 1990; 48: 9-19.

62. Berentein A, Lasjaunias P. Surgical neuroangiography. Vol 4. Springer, Berlin Heidelberg New York Tokyo, 1991.

63. Berman MF, Sciacca RR, Pile-Spellman J et al. The epidemiology of brain arteriovenous malformations. Neurosurgery 2000; 47: 389-396.

64. Crawford PM, West CR, Chadwick DW, Shaw MD. Arteriovenous malformations of the brain: natural history in unoperated patients. J Neurol Neurosurg Psychiary 1986; 49: 1-10.

65. Ondra SL, Trouppp H, George ED, Schwab K. The natural history of symptomatic arteriovenous malformations of the brain: a 24-year follow up assessment. J Neurosurg 1990; 73: 387-392.

66. Wikholm G. Occlusion of cerebral arteriovenous malformations with N-butyl cyanoacrylate is permanent. AJNR Am J Neuroradiol 1995; 16: 479-482.

67. Hofmeister C, Stapf C, Hartmann A, et al. Demographic, morphological and clinical characteristics of 1289 patients with brain arteriovenous malformation. Stroke 2000; 31: 1307-1310.

68. The Arteriovenous Malformation Study Group. Arteriovenous malformations of the brain in adults. N Engl J Med 1999; 340: 1812-1818.

69. Yamada D. Arteriovenous malformations in the functional area: surgical treatment and regional cerebral blood flow. Neurol Res 1982; 4: 283-322.

70. Graf CJ, Perret GE, Torner JC. Bleeding from cerebral arteriovenous malformations as part of their natural history. J Neurosurg 1983; 37: 331-337.

71. Wilkins RH. Natural history of intracranial vascular malformations. A review. Neurosurgery 1985; 16: 421-430.

72. Willinsky R, Lasjaunias P, TerBrugge K, et al. Brain arteriovenous malformations. Analysis of angio-architecture in relationship to hemorrhage. J Neuroradiol 1988; 15: 225-237.

73. Gracia- Monaco R, Alvarez H, Goulao Z, Pruvost Ph, Lasjaunias P. Posterior fossa arteriovenous malformations. Angioarchitecture in relation to their hemorrhagic episodes. Neuroradiology 1990; 31: 471-475.

74. Spetzler RF, Hargraves RW, McCormick PW, Zabramski JM, Flom RA, Zimmerman RS. Relationship of perfusion pressure and size to risk of hemorrhage from arteriovenous malformations. J Neurosurg 1992; 76: 918-923.

75. Marks MP, Lane B, Steinberg G, Chay P. Hemorrhage in intracerebral AVMs: Angiographic determinants. Radiology 1990; 176: 807-813.

76. Duong DH, Young WL, Vang MC, et al. Feeding artery pressure and venous drainage pattern are primary determinants of hemorrhage from cerebral arteriovenous malformations. Stroke 1998; 29: 1167-1176.

77. Yasargil MG. Pathologic considerations. In: Yasaogil MG (ed) Microneurosurgery, AVM of the brain: history, embryology, pathologic

considerations, hemodynamics, diagnostic studies, microsurgical anatomy, vol 3A. Thieme, New York, 1987; p. 49-211.

78. Frishberg BM. Neuroimaging in presumed primary headache disorders. Semin Neurol 1997; 17: 373-382.

79. Carter LP, Gumerlock MK. Steal and cerebral arteriovenous malformations. Stroke 1995; 26: 2371-2372.

80. Mandybur TI, Nazek M. Cerebral arteriovenous malformations. A detailed morphological and immunohistochemical study using actin. Arch Pathol Lab Med 114: 970-973, 1990.

81. Nazek M, Mandybur TI, Kashiwagi S. Oligodendroglial proliferative abnormality associated with arteriovenous malformation: report of three cases with review of the literature. Neurosurgery 23:781-785, 1988.

82. McCormick WF. The pathology of vascular (arteriovenous) malformations. J Neurosurgery 24:807-816, 1966.

83. Lasjaunias P, terBrugge KG, Berenstein A. Introduction and general comments regarding pediatric intracranial arteriovenous shunts. In: surgical neuroangiography. Vol. 3, Berlin/Heidelberg: Springer-Verlag: 2006, p. 27-104.

84. Lim M, Cheshier S, Steinberg GK. New vessel formation in the central nervous system during tumor growth, vascular malformations, and Moyamoya. Curr Neurovasc Res 2006; 3: 237–245.

85. Shenkar R, Elliott JP, Diener K, Gault J, Hu LJ, Cohrs RJ, et al. Differential gene expression in human cerebrovascular malformations. Neurosurgery 2003; 52: 465–468.

86. Moftakhar P, Hauptman JS, Malkasian D, Martin NA. Cerebral arteriovenous malformations. Part 1: cellular and molecular biology. Neurosurg Focus 2009; 26(5): E10.

87. Lim M, Haddix T, Harsh GR, Vogel H, Steinberg GK, Guccione S. Characterization of the integrin alpha v beta3 in arteriovenous malformations and cavernous malformations. Cerebrovasc Dis 2005; 20: 23–27.

88. Seker A, Yildirim O, Kurtkaya O, Sav A, Gunel M, Pamir MN, et al. Expression of integrins in cerebral arteriovenous and cavernous malformations. Neurosurgery 2006; 58: 159–168.

89. Sternlicht MD, Werb Z. How matrix metalloproteinases regulate cell behavior. Annu Rev Cell Dev Biol 2001; 17: 463–516.

90. Hashimoto T, Mesa-Tejada R, Quick CM, Bollen AW, Joshi S, Pile-Spellman J, et al: Evidence of increased endothelial cell turnover in brain arteriovenous malformations. Neurosurgery 2001; 49: 124–131.

91. Hatva E, Jaaskelainen J, Hirvonen H, Alitalo K, Haltia M: Tie endothelial cell-specific receptor tyrosine kinase is upregulated in the vasculature of arteriovenous malformations. J Neuropathol Exp Neurol 1996; 55: 1124–1133.

92. Sure U, Butz N, Schlegel J, Siegel AM, Wakat JP, Mennel HD, et al: Endothelial proliferation, neoangiogenesis, and potential de novo generation of cerebrovascular malformations. J Neurosurg 2001; 94: 972–977.

93. van der Loop FT, Schaart G, Timmer ED, Ramaekers FC, van Eys GJ: Smoothelin, a novel cytoskeletal protein specific for smooth muscle cells. J Cell Biol 1996; 134: 401–411.

94. Achrol AS, Guzman R, Varga M, Adler JR, Steinberg GK, Chang SD. Pathogenesis and radiobiology of brain arteriovenous malformations: implications for risk stratification in natural history and posttreatment course. Neurosurg Focus 2009; 26(5): E9.

95. Ducreux D, Trystram D, Oppenheim C, et al. Imagerie diagnostique des malformations arterio-veineuses cerebrales. Neurochirurgie 2001; 47:190-200.

96. Delgado Almandoz JE, Schaefer PW, Forero NP, et al. Diagnostic accuracy and yield of multidetector CT angiography in the evaluation of spontaneous intraparenchymal cerebral hemorrhage. AJNR Am J Neuroradiol 2009; 30(6): 1213-1221.

97. Romero JM, Artunduaga M, Forero NP, et al. Accuracy of CT angiography for the diagnosis of vascular abnormalities causing intraparenchymal hemorrhage in young patients. Emerg Radiol 2009; 16: 195–201.

98. Choi IS, Erdem E. Mobile CT in neurointerventional suite. Medica mundi 1999; 43(4): 45-50.

99. Edelman RR, Wentz KU, Mattle HP, et al. Intracerebral arteriovenous malformations: evaluation with selective MR angiography and venography. Radiology 1989; 173: 831-837.

100. Petkova M, Gauvrit JY, Trystram D, et al. Three-dimensional dynamic time-resolved contrast-enhanced MRA using parallel imaging and a

variable rate *k*-space sampling strategy in intracranial arteriovenous malformations. J Magn Reson Imaging 2009; 29: 7-12.

101. Dabus G, Getch CG, Batjer HH, et al. 4D Radial Acquisition Contrast-Enhanced MR Angiography and Intracranial Arteriovenous Malformations: Quickly Approaching Digital Subtraction Angiography. *Stroke* 2009; 40: 2749-2753.

102. Taschner CA, Gieseke J, Thuc VL, et al. Intracranial arteriovenous malformation: time-resolved contrast-enhanced MR angiography with combination of parallel imaging, keyhole acquisition, and k-space sampling techniques at 1.5 T. Radiology 2008; 246(3): 871-879.

103. Hadizadeh DR, Falkenhausen MV, Gieseke J, et al. Cerebral arteriovenous malformation: Spetzler-Martin classification at subsecond-temporal-resolution four-dimensional MR angiography compared with that at DSA. Radiology 2008; 246(1): 205-213.

104. Heidenreich JO, Schilling AM, Unterharnscheidt F, et al. Assessment of 3D-TOF-MRA at 3.0 Tesla in the Characterization of the Angioarchitecture of Cerebral Arteriovenous Malformations: A Preliminary Study. Acta Radiologica 2007; 48(6): 678-686.

105. Maldjian J, Atlas SW, Howard RS, et al. Functional magnetic resonance imaging of regional brain activity in patients with intracerebral arteriovenous malformations before surgical or endovascular therapy. J Neurosurg 1996: 84: 477-483.

106. Schlosser MJ, McCarthy G, Fullbright RK, et al. Cerebral vascular malformations adjacent to sensorimotor and visual cortex: functional magnetic resonance imaging studies before and after therapeutic intervention. Stroke 1997; 28: 1130-1137.

107. Berube J, Mc Laughlin N, Bourgouin P, et al. Diffusion tensor imaging analysis of long association bundles in the presence of an arteriovenous malformation. J Neurosurg 2007; 107: 509-514.

108. Nakstad PH, Nornes H. Superselective angiography, embolization and surgery in treatment of arteriovenous malformations of the brain. Neuroradiology 1994; 36: 410-413.

109. Berger MO, Anxionnat R, Kerrien E, et al. A methodology for validating a 3D imaging modality for brain AVM delineation: Application to 3DRA. Comput Med Imaging Graph 2008; 32: 544-553.

110. Kakizawa Y, Nagashima H, Oya F, et al. Compartments in arteriovenous malformation nidi demonstrated with rotational three-

dimensional digital subtraction angiography by using selective microcatheterization: Report of three cases. J Neurosurg 2002; 96: 770-774.

111. Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. J Neurosurg 65:476-483, 1986.

112. Martin N, Vinters H. Pathology and grading of intracranial vascular malformations. In: Barrow DL (ed) Intracranial vascular malformations. Neurosurgical topics. American Association of Neurological Surgeons. Park Ridge, Illinois, 1990; p. 1-30.

113. Fleetwood IG, Steinberg GK. Arteriovenous malformations. Lancet 2002; 359: 863-873.

114. Mattle HP, Schroth G, Seiler RW. Dilemmas in the management of patients with arteriovenous malformations. J Neurol 2000; 247: 917-928.

115. Ogilvy CS, Stieg PE, Awad I, Brown RD Jr, Kondziolka D, Young WL, Hademenos G. Special writing group of the stroke council, American Stroke association: AHA Scientific statement: Recommendations for the management of intracranial arteriovenous malformations: Stroke 2001; 32: 1458-1471.

16. Hamilton MG, Spetzler RF. The prospective application of a grading system for arteriovenous malformations. Neurosurgery 1994; 34: 193-200.

17. Sirin S, Kondziolka D, Niranjan A, Flickinger JC, Maitz AH, Lunsford LD: Prospective staged volume radiosurgery for large arteriovenous malformations: Indications and outcomes in otherwise untreatable patients. Neurosurgery 2006; 58: 17-27.

18. Fiehler J, Stapf C. ARUBA – beating natural history in Unruptured brain AVMs by intervention. Neuroradiology 2008; 50: 465-467.

19. Luessenhop AJ, Gibbs M, Velasquez AC. Cerebrovascular response to emboli. Observations in patients with arteriovenous malformations. Arch Neurol 1962; 7: 264-274.

20. Luessenhop AJ, Velasquez AC. Observations on the tolerance of the intracranial arteries to catheterisation. J Neurosurg 1964; 21: 84-91.

21. Luessenhop AJ, Kachmann R, Shevlin W, et al. Clinical evaluation of artificial embolization in the management of large cerebral arteriovenous malformations. J Neurosurg 1965: 23: 400-417.

22. Dolace G. Uber eine neue Methode: Der Arterien-Katheterismus des Gehirns. Psychopharmacologia 1964; 5: 313-316.

123. Yodh S, Perce NT, Weggel RJ, Montgomery DB. A new system for intravascular navigation. Med Biol Eng 1968; 6: 143-147.

124. Hilal SK. Catheter with a magnetic tip for cerebral angiography. Med Tribune 1969; 2: 1.

125. Kricheff II, Madayag M, Braunstein P. Transfemoral catheter embolization of cerebral and posterior fossa arteriovenous malformations. Radiology 1972; 103: 107-111.

126. Hilal SK, Michelsen JW. Therapeutic percutaneous embolization for extraaxial vascular lesions of head, neck and spine. J Neurosurg 1975; 43(3): 275-87.

127. Djindjian R, Houdart R. Arteriographie superselective de la carotide interne et embolisation. Rev Neurologique 1975; 131: 829-846.

128. Berenstein A. Technique for catheterization and embolization of the lenticulostriate arteries. J Neurosurg 1981; 54: 783-789.

129. Debrun GM, Vinuela FV, Fox AJ, Kan S. Two different calibrated leak balloons: Experimental work and application in human. AJNR Am J Neuroradiol 1982; 3: 407-414.

130. Kikuchi T, Strother CM, Boyer M. New catheter for endovascular interventional procedures. Radiology 1987; 165: 870-871.

131. Dion JE, Duckwiler GR, Lyly P, Vinuela F, Bentson J. progressive suppleess pursil catheter: A new tool for superselective angiography and embolization. AJNR Am J Neuroradiol 1989; 10: 1068-1070.

132. Germano IM, Davis RL, Wilson CB, et al. Histopathological follow-up study of 66 cerebral arteriovenous malformations after therapeutic embolization with polyvinyl alcohol. J Neurosurg 1992; 76: 607-614.

133. DeMeritt JS, Pile-Spellman J, Mast H, et al. Outcome analysis of preoperative embolization with n-Butyl cyanoacrylate in cerebral arteriovenous malformations. AJNR Am J Neuroradiol 1995; 16: 1801-1807.

134. Grzyska U, Westphal M, Zanella F, Freckmann N, Herrmann HD, Zeumer H (1993) A joint protocol for the neurosurgical and neuroradiologic treatment of cerebral arteriovenous malformations: indications, techniques and results in 76 cases. Surg Neurol 1993; 40: 476–484.

135. Kerber C. Intracranial cyanoacrylate: a new catheter therapy for arteriovenous malformation. Invest Radiol 1975; 10: 536–538.

136. Kerber CW, Cromwell LD, Sheptak PE. Intraarterial cyanoacrylate: an adjunct in the treatment of spinal/paraspinal arteriovenous malformations. AJR Am J Roentgenol 1978; 130: 99–103.

137. Cromwell LD, Harris AB. Treatment of cerebral arteriovenous malformations: a combined neurosurgical and neuroradiological approach. J Neurosurg 1980; 52: 705–708.

138. Samson D, Ditmore QM, Beyer CW. Intravascular use of isobutyl 2-cyanoacrylate in the treatment of intracranial arteriovenous malformations. Neurosurgery 1981; 8: 43–51.

139. Pevsner PH, George ED, Doppman JL. Interventional radiology polymer update: acrylic. Neurosurgery 1982; 10: 314–316.

140. Vinuela F, Fox AJ. Intervetnional neuroradiology and the management of arteriovenous malformations and fistulas. Neurol Clin 1983; 1: 131–154.

141. Brothers MF, Kaufman JC, Fox AJ, Deneikis JP. N-butyl-2-cyanoacrylate: substitute for IBCA in interventional neuroradiology. AJNR Am J Neuroradiol 1989; 10: 777–786.

142. Gyurko G, Szucs J, Ezsely F, Koja C. Use in vascular surgery of the tissue adhesive histocryl. Acta Chir Hung 1974; 15: 353–360.

143. Matsumoto T, Nemhauser GM, Soloway HB. Cyanoacrylate tissue adhesives: an experimental and clinical evaluation. Mil Med 1986; 134: 247–252.

144. Debrun GM, Aletich V, Ansman JI, et al. embolization of the nidus of brain arteriovenous malformations with n-butyl cyanoacrylate. Neurosurgery 1997; 40: 12-121.

145. Leonardi M, Barbara C, Simonetti L, et al. Glubran 2: a new acrylic glue for neuroradiological endovascular use: experimental study on animals. Interventional Neuroradiology 2002; 8: 245-250.

146. Desal HA, Toulgoat F, Raoul S, et al. Brain arteriovenous malformations: technical note of endovascular treatment with Glubran. Interventional Neuroradiology 2005; 11: 125-130.

147. Raffi L, Simonetti L, Cenni P, Leonardi M. Use of Glubran 2 acrylic glue in interventional neuroradiology. Neuroradiology. 2007; 49(10): 829-36.

148. Lundqvist C, Wikholm G, Svendsen P. Embolization of cerebral arteriovenous malformations: part II-aspects of complications and late outcome. Neurosurgery 1996; 39:460-67.

149. Chaloupka JC, Vinuela F, Vinters HV, Robert J. Technical feasibility and histopathologic studies of ethylene vinyl copolymer (EVAL) using a swine endovascular embolization model. AJNR Am J Neuroradiol 1994; 15(6): 1107-1115.

150. Sampei K, Hashimoto N, Kazekawa K, et al. Histological changes in brain tissue and vasculature after intracarotid infusion of organic solvents in rats. Neuroradiology 1996; 38: 291-294.

151. Murayama Y, Vinuela F, Ulhoa A et al. Nonadhesive liquid embolic agent for cerebral arteriovenous malformations: preliminary histopathological studies in swine rete mirabile. Neurosurgery 1998; 43: 1164-1175.

152. Chaloupka JC, Huddle DC, Alderman J et al: A Reexamination of the angiotoxicity of superselective injection of DMSO in the swine rete embolization model. AJNR Am J Neuroradiol 1999; 20: 401-410.

153. Valavanis A, Pangalu A, Tanaka M. Endovascular treatment of cerebral arteriovenous malformations with emphasis on curative role of embolisation. Schweizer Archiv für Neurologie und Psychiatrie 2004; 155(7): 341-347.

154. Joint writing group of the technology assessment committee, American society of interventional and therapeutic neuroradiology; Joint section on cerebrovascular neurosurgery, a section of the American association of neurological surgeons and congress of neurological surgeons; and Section of stroke and the Section of interventional neurology of American academy of neurology. Reporting terminology of brain arteriovenous malformation: clinical and radiographic features for use in clinical trials. Stroke 2001; 32: 1430-1442.

155. Saleh RS, Singhal A, Lohan D, et al. Assessment of cerebral arteriovenous malformations with high temporal and spatial resolution contrast-enhanced magnetic resonance angiography: a review from protocol to clinical application. Top Magn Reson Imaging 2008; 19(5): 251-7.

156. Lee KE, Choi CG, Choi JW, et al. Detection of residual brain arteriovenous malformations after radiosurgery: diagnostic accuracy of contrast-enhanced three-dimensional time of flight MR angiography at 3.0 Tesla. Korean J Radiol 2009; 10: 333-339.

157. Purdy PD, Batjer HH, Samson DS: Management of hemorrhagic complications from preoperative embolization of arteriovenous malformations. J Neurosurg 1991; 74: 205-211.

158. Picard L, Da Costa E, Marchal JC et al: Acute spontaneous hemorrhage after embolization of brain arteriovenous malformations with N-butyl cyanoacrylate. J Neuroradiol 2001; 28: 147-165.

159. Kwam DA, Michelsen J, Quest DO. Intracerebral hemorrhage as a complicaton of artificial embolization. Neurosurgery 1980; 7: 491-494.

160. Massoud TF, Hademenos GJ, Young WL, Gao E et al: Can induction of systemic hypotension help prevent nidus rupture complicating arteriovenous malformation embolization? Analysis of underlying mechanism achieved using a theoretical model. AJNR Am J Neuroradiol 2000; 21: 1255-1267.

161. Sorimachi T, Takeuchi S, Koike T, Minakawa T, Tanaka R: Blood pressure monitoring in feeding arteries of cerebral arteriovenous malformations during embolizations: A preventive role in hemodynamic complications. Neurosurgery 1995; 37: 1041-1048.

162. Hademenos GJ, Massoud TF: Risk of intracranial arteriovenous malformation rupture due to venous drainage impairment: a theoretical analysis. Stroke 1996; 27: 1072-1083.

163. Bradac GB, Bergui M, Stura G: Endovascular treatment of brain arteriovenous malformations. Rivista di Neuroradiologia 2001; 14: 373-380.

164. Spetzler RF, Wilson CB, Weinstein P, Mehdom M, Townsend J: Normal perfusion pressure breakthrough theory. Clin Neurosurg 1978; 25: 651-672.

165. Duckwiler GR, Dion JE, Vinuela F, Reichman A: Delayed venous occlusion following embolotherapy of vascular malformations in the brain. AJNR Am J Neuroradiol 1992; 13: 1571-1579.

166. Vinuela F, Fox AJ, Debrun G, Drake CG et al: Progressive thrombosis of brain arteriovenous malformations after embolization with isobutyl 2-cyanoacrylate. AJNR Am J Neuroradiol 1983; 4: 1233-1238.

167. Ledezma CJ, Hoh BL, Carter BS et al: Complications of cerebral arteriovenous malformation embolization: Multivariate analysis of predictive factors. Neurosurgery 2006; 58: 602-611.

168. Piotin M, Ross IB, Weill A et al: Intracranial arterial aneurysms associated with arteriovenous malformations: endovascular treatment. Radiology 2001; 220: 506-513.

169. Gao E, Young WL et al: Cerebral arteriovenous malformation feeding artery aneurysms: a theoretical model of intravascular pressure changes after treatment. Neurosurgery 1997; 41: 1356-1358.

170. Li TL, Fang B, He XY, Huan YI et al: Complication analysis of 469 brain arteriovenous malformations treated with n-butyl cyanoacrylate. Interventional neuroradiology 2005; 11: 141-148.

171. Hartmann A, Pile-Spellman J et al: Risk of endovascular treatment of brain arteriovenous malformations. Stroke 2002; 33: 1816-1820.

172. Júnior AM, Arrais CA, Saboya R, Velasques RD, Junqueira PL, Dulley FL. Neurotoxicity associated with dimethylsulfoxidepreserved hematopoietic progenitor cell infusion. Bone Marrow Transplant 2008; 41: 95–96.

173. Gruber A, Mazal PR, Bavinzski G, Killer M et al: Repermeation of partially embolized cerebral arteriovenous malformations: A clinical, radiologic, and histologic study. AJNR Am J Neuroradiol 1996; 17:1323-1331.

174. VR Rao, KR Mandalam, AK Gupta, S kumar, S Joseph: Dissolution of isobutyl 2-cyanoacrylate on long-term follow-up. AJNR Am J Neuroradiol 1989; 10: 135-141.

175. Lagares A, Lobato RD, Campollo J, Gomez PA et al: Embolizacion de MAVs coadyuvante de cirugia o radiocirugia. Neurocirugia (Astur) 2000; 11: 271-280.

176. Vinter HV, Lundie MJ, Kaufmann JC: Long-term pathological follow-up of cerebral arteriovenous malformations treated by embolization with bucrylate. N Engl J Med 1986; 314: 477-483.

177. Higashida RT: Embolization of arteriovenous malformations with Onyx: Clinopathological experience in 23 patients. Neurosurgery 2001; 48: 985.

178. Akin ED, Perkin E, Ross IB. Surgical handling characteristics of an ethylene vinyl alcohol copolymer compared with n-butyl cyanoacrylate used for embolization of vessels in an arteriovenous malformation resection model in swine. J Neurosurg 2003; 98: 366-370.