Clinicoradiologic Spectrum and Endovascular Management of Brain Arteriovenous Malformations

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DECLARATION

I hereby declare that this thesis titled **"Clinicoradiologic Spectrum and Endovascular Management of Brain Arteriovenous Malformations''** has been prepared by me under the supervision and guidance of Dr Kapilamoorthy T R, (Professor & Head) and Dr. Jayadevan ER, (Assistant Professor), Department of Imaging Sciences and Interventional Radiology, Sree Chitra Institute for Medical Sciences and Technology, Thiruvananthpuram.

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CERTIFICATE

This is to certify that the work incorporated in this thesis titled "Clinicoradiologic Spectrum and Endovascular Management of Brain Arteriovenous Malformations'' for the degree for DM (NEUROIMAGING AND INTERVENTIONAL NEURORADIOLOGY) has been carried out by Dr. Atul Mishra under my supervision and guidance. The work done in connection with this thesis has been carried out by the candidate himself and is genuine.

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CONTENTS

Introduction

Arteriovenous malformations of the brain (brain AVMs) correspond to congenital cerebrovascular anomalies , also known as intracerebral AVMs. These are relatively rare central nervous system lesions that are the cause of significant long-term morbidity and mortality. These were first described about a century ago and have been considered to be difficult entity to manage surgically.

AVMs can clinically present with seizures, headache, focal neurodeficits and life threatening intracranial hemorrhage. In the symptomatic group, AVMs are increasingly being recognized as a possibly treatable cause of various neurologic manifestations produced. More and more clinically silent AVMs are also being diagnosed due to advances in Imaging. Annual average risk of hemorrhage in such cases stated is 1-2%.

Current therapeutic options include microvascular neurosurgery, stereotactic radiation (radiosurgery), and endovascular embolization. Embolization is an important, well-established modality for brain AVM treatment that is usually combined with surgery or stereotactic radiosurgery and occasionally may even be used as a standalone treatment. Embolization is, however, associated with significant risks that must be carefully balanced against the potential benefits in each patient.

Luessenhop and Spence first introduced the embolization of cerebral AVMs in 1960, and the transfemoral approach has been used to embolize brain AVMs. Since then, embolization of vascular lesions in the brain has developed as an important specialty. Various agents have been used for embolization in past including silk threads, coils,ethanol, PVA particles with limited success and high rates of recurrence. In the recent years, use of liquid embolic agents such as NBCA was in vogue with relatively better embolization and practically no recurrence. However, NBCA requires significant technical skill and poor control during injection. In 1990 Taki, et al.,developed the original formulation of Onyx (Onyx Liquid Embolic

System; Micro Therapeutics, Inc., Irvine, CA) which is a new co-polymer (EVOH) with proclaimed better penetration and controlled, prolonged injection. This new agent has made embolization technically less demanding and is claimed to have better nidus obliteration rates.

Available data which is mostly western, has been generally applied to our context regarding clinical presentation. Management strategies also differ as economic and technical considerations are different.Moreover, the management strategies worldwide have also been in continuous evolution due to technological advances (microcatheters/ imaging system/ embolizing materials).This study will try to analyze these issues by assessing the clinical and radiological characteristics, angiographic and clinical outcome of various methods of embolization, procedure outcome and complications , if any.

Aims and Objectives

This is a retrospective study to analyze clinical & radiological characteristics, efficacy of management by embolization and complications of management (if any) in all the patients with brain arterio-venous malformations (AVMs) who reported to SCTIMST between 1 Jan 2005 – 31 Oct 2011. The objectives of the study were as follows:-

1. To describe clinical and radiological features in patients with brain AVM for better understanding the natural history of AVM
2. To assess the effectiveness of embolization for brain AVM.
3. To find out difficulties and complications during management of AVM
4. To evaluate radiologic & clinical outcome in patients treated with embolization

Review of Literature

INTRODUCTION

Brain arteriovenous malformations (AVMs) are relatively rare central nervous system lesions that are the cause of significant long-term morbidity and mortality. Current therapeutic options include microvascular neurosurgery, stereotactic radiation (radiosurgery), and endovascular embolization. Embolization is an important, well-established modality for brain AVM treatment that is usually combined with surgery or stereotactic radiosurgery. Embolization is, however, associated with significant risks that must be carefully balanced against the potential benefits in each patient. Embolization performed by experienced interventional neuroradiologists in appropriately selected cases improves the overall safety and efficacy of brain AVM treatment.

CLASSIFICATION AND PATHOGENESIS OF CEREBRAL VASCULAR MALFORMATIONS

Cerebral vascular malformations have been studied since the 18th century. Nonetheless, clinically useful classification schemes have only been developed recently. Initially, vascular malformations were categorized by their gross pathological appearance, resulting in confusing and contradictory nomenclature that

created a barrier to understanding their etiology, natural history, and clinical management (1).

A new biological classification for vascular lesions was proposed in 1982 (2). Two major categories were identified: hemangiomas and vascular malformations. Lesions with growth potential shown by proliferation of endothelial cells with active DNA

synthesis were defined as hemangiomas and were considered vascular neoplasms. Lesions without endothelial cell proliferation or active DNA synthesis and displaying proportionate growth were named vascular malformations and were thought to be hamartomas rather than neoplasms. Vascular malformations were subdivided into arterial, capillary, venous, lymphatic and combined types (2).

Four categories of intracranial vascular malformations have been defined on the basis of gross and microscopic pathological data: AVM, capillary telangiectasia, cavernous malformation, and venous malformation (3–5). A mixed malformation also has been described (6). These have been considered congenital lesions, present from birth without the potential for significant cellular proliferation or de novo postnatal development.

Brain AVMs have cerebral arterial feeders directly connected to the venous system without an intervening capillary bed, resulting in high-flow arteriovenous (AV) shunts. The nidus (Latin for nest) contains the direct AV connections. The vessels in the nidus vary in size and histology from relatively well-differentiated arteries and veins to thick and thin walled, hyalinized, malformed vessels that are neither. Dilated segments of vessels commonly occur. There is gliotic brain parenchyma within and around the nidus. Gross or microscopic calcification may be present with the vascular walls or in the gliotic parenchyma. Hemosiderin is commonly present, indicative of some degree of prior hemorrhage. The gross pathological appearance has been aptly described as a ‘‘bag of worms’’ (5).

Most brain AVMs occur sporadically; however,they also are associated with a number of congenital or hereditary syndromes, including: Rendu-Osler-Weber syndrome (hereditary hemorrhagic telangiec- tasia), Klippel-Trenaunay syndrome, Parks-Weber syndrome, Wyburn-Mason syndrome, and Sturge-Weber disease (7). Rare familial cases not associated with syndromes also have been described (8).

There is recent evidence that not all brain AVMs are congenital in origin (7). Although the large majority probably occurs congenitally because of the failure of capillary formation during early embryogenesis (9), some brain AVMs appear to form in response to a postnatal stimulus of angiogenesis, particularly inyounger patients. The de novo development of brain AVMs in a child (10) and in an adult (11) has been reported. Also, brain AVMs have reoccurred in children after complete surgical resection (12).

EPIDEMIOLOGY OF BRAIN AVMs

Most of the estimates of the prevalence of brain AVMs are flawed and potentially inaccurate. The widely quoted prevalence estimates of 500 to 600/100,000 were based on biased autopsy data. Another erroneous estimate of 140/100,000 was based on an inappropriate analysis of the Cooperative Study of Intracranial Aneurysm and Subarachnoid Hemorrhage data. These estimates may represent greater than 10-fold overestimates of the true prevalence (13). A comprehensive review of the published literature performed in 2001 identified only three population based studies of the incidence and/or prevalence of brain AVMs, all retrospective in nature (14). The Mayo Clinics identified a total of 48 intracranial vascular malformations in the population of Olmstead County, Minnesota, over a period of 27 years, from 1965 to 1992. The brain AVM detection rate was 1.11 (95% CI, 0.7–1.5) per 100,000 person-years (15). The incidence of symptomatic brain AVMs was 1.1 (95% CI, 0.6–1.8) per 100,000 patient-years in the Leeward Islands of the Netherlands Antilles between 1980 and 1990 (16). A retrospective study in the Lothian region of Scotland found a minimum point prevalence of 15 symptomatic brain AVMs per 100,000 in unselected living adults (17,18). In 2003, a prospective population based study of brain AVMs in the New York

Islands (Manhattan, Staten Island, and Long Island) with 9.4 million residents reported an AVM detection rate of 1.34 (95% CI, 1.18–1.49) per 100,000 person-years.

The estimated prevalence of brain AVM hemorrhage within the detected cases was 0.68 (95% CI, 0.57–0.79) per 100,000 (19). The currently available data do not suggest that there is a large reservoir of asymptomatic brain AVMs in the general population, but that most brain AVMs become symptomatic during life (20).

NATURAL HISTORY OF BRAIN AVMs

The risks of treating a brain AVM must be weighed against the natural history of the disease, in particular the possibility that a brain AVM will hemorrhage or rehemorrhage if it is not treated and the associated potential clinical consequences. Unfortunately, little unbiased natural history data are available, in part, because brain AVMs are relatively rare and quite heterogeneous and also because most undergo some form of treatment. No level I or level II natural history studies have been published (21). Data on specific predictors for the clinical course of a specific brain

AVM are even more limited. In many natural history studies there is a selection bias toward untreatable AVMs. In addition, natural history outcomes usually have not been correlated with the type of presentation, the analyses have differed and follow up periods have been short (14).

Despite these limitations, some general observations can be made about the natural history of brain AVMs. Clinical presentation can occur at any age, with the mean age of presentation in the fourth decade of life. There is an essentially equal distribution between sexes (14). Brain AVMs most commonly present with intracranial hemorrhage, epilepsy, headache, or a

focal neurological deficit, although they are occasionally found incidentally (14). Intracranial hemorrhage is the most common form of clinical presentation (21). In a prospective population-based study published in 1996, 65% of patients newly diagnosed with a brain AVM presented with intracranial hemorrhage (22). Intraparenchymal hemorrhage occurred in 41% of these cases, subarachnoid hemorrhage in 24%, intraventricular hemorrhage in 12%, and a combination of these types in 23% of cases. The more recent prospective population-based study of brain AVMs in the New York Islands reported that 38% of patients with newly found AVMs presented with intracranial hemorrhage (19).

Hospital-based case series have been retrospectively analyzed to identify risk factors for brain AVM hemorrhage (14). These findings have not been confirmed by prospective population-based studies. The features most consistently associated with an increased risk of hemorrhage include deep venous drainage, a single draining vein, venous stenoses, and high-feeding mean arterial pressure (14). These may share the common hemodynamic mechanism of associated high intranidal pressures (23). Less consistent risk factors for hemorrhage are a small AVM size, feeding artery and intranidal aneurysms, and deep or posterior fossa locations (14). Sex and pregnancy do not appear to increase the risk of hemorrhage (24).

Features that may be associated with a decreased risk of hemorrhage include a large AVM size (25), arterial stenosis and ectasia (26), dural arterial supply (27), venous recruitment (28), and angiogenesis (29).

The second most common form of clinical presentation is epilepsy. In one retrospective population-based study, 19% of newly discovered AVMs presented with seizures (22). In two retrospective hospital-based studies, 18% and 27% of AVMs presented with seizures, respectively (30,31).

Other less common brain AVM presentations include headache (1% and 11% in two hospital-based series) (30,31), focal neurological deficit (7%

and 5% in two hospital-based series) (30,31), and as an incidental finding in an asymptomatic individual (15% in one population-based study, 0% and 3% in two hospital based series) (22,30,31).

There are extremely limited data on the natural history of brain AVMs following the initial diagnosis.An annual 2% to 4% risk of first-ever hemorrhage from a brain AVM is widely quoted on the basis of a few hospital-based series (30,32–35). No prospective, population-based study of the clinical course of unruptured brain AVMs has been published (14). After an initial bleed, the risk for recurrent hemorrhage may be as high as 18% in the first year (31). This appears to subsequently decrease to the baseline 2% to 4% annual risk of hemorrhage over time (36).

Fatality rates from brain AVM hemorrhage range from 0% to 18% during the first year (22,30,31,35,37). 276 Weigele et al.The reported long-term annual fatality rates are 1% to 1.5% (30,35). Ondra et al. prospectively evaluated 166 untreated symptomatic brain AVM patients over a mean follow-up period of 23.7 years. There was a 4.0% annual rate of hemorrhage and a 1.0% annual mortality rate. The combined rate of mortality and major morbidity was 2.7% per year. Over the follow up period, 23% of the patients died from hemorrhage.

The incidence of bleeding and death were the same whether the AVM initially presented with hemorrhage (35). Recurrent hemorrhage appears to cause a morbidity rate similar to the initial bleed (36). In another hospital-based study, 47% of patients with a first-ever hemorrhage sustained no neurological defect and 37% experienced no significant disability despite symptoms (Rankin 1) (37). Parenchymal hemorrhage had a greater likelihood (52%) of producing a neurological defect.

To provide evidence based answers to many of the management issues associated with the AVMs , a randomized multicenter trial ARUBA (A Randomized trial of Unbled AVMs) has been started with the support of

NINDS. Begun in April 2007 with 3 centers, the trial has grown to 65 centers, and has randomized 124 patients through mid-June 2010 en route to the planned 400. On completion, the trial is expected to lay the foundation for strong evidence based management , especially of unbled AVMs (154).

In our series the commonest presenting feature was seizures (33 patients, 44%) next was hemorrhage (25 patients, 32%), then head ache (11patients, 14%) followed by weakness and non specific complaints (9 patients, 11%). This is at slight variance with literature where hemorrhage is quoted as more common than epilepsy.

ANGIOGRAPHY AND ANGIOARCHITECTURE OF BRAIN AVMs

(A) Selective and Superselective Cerebral Angiography

Brain AVMs demonstrate AV shunting on angiography, resulting in early opacification of the draining veins and a decrease in the AV transit time (38). This shunting is the result of a direct connection between the arterial and venous sides of the cerebral circulation without an intervening capillary bed. There may be two types of AV connections: fistulous and plexiform (39). A fistulous nidus contains large-caliber direct AV connections. A plexiform nidus consists of a conglomerate of multiple smaller and more numerous vascular channels supplied by one or more arterial feeders . These are collected into one or more draining veins. A plexiform nidus can contain one or more direct fistulas (mixed plexiform-fistulous nidus; (39,40).

The complete angiographic evaluation of a brain AVM consists of :-

(1) the ***selective*** evaluation of the AVM and the entire cerebral circulation using 4 or 5 French (Fr) diagnostic catheters and (2) the ***superselective*** angiographic evaluation of the feeding arterial pedicles, the nidus, and the venous drainage using microcatheters advanced into distal aspects of the arterial feeders (38).

The goals of the selective angiographic evaluation are listed in Table 1. This provides an important assessment of the arterial supply to the AVM, the general characteristics of the nidus, the venous drainage of the AVM, and the rest of the intracranial circulation. Selective angiography, however, has significant limitations. Rapid AV shunting often superimposes the arterial feeders, the nidus, and the draining veins obscuring important features, such as small arterial feeders, distal feeding pedicles, nidal aneurysms, direct AV fistulas, and small accessory draining veins (38).

The goals of superselective angiography are listed in Table 2. Such detailed anatomic information from superselective angiography concerning the dista arterial feeders, the nidus, and the proximal draining veins is critical for planning and performing endovascular embolizations (38).

Table 1 Goals of Selective Angiographic Evaluation of Brain AVMs

1. Arterial territories supplying the AVM 2. Feeding pedicles 3. High-flow arteriopathy (stenoses, ectasias, flow-related aneurysms) 4. Nidus (size, shape, location, flow, fistulas, ectasias, aneurysms) 5. Venous drainage (territories, deep, superficial) 6. Individual draining veins 7. High-flow venous angiopathy (dural sinuses, venous stenoses, occlusions, and varices) 8. Venous drainage of normal brain parenchyma Abbreviation: AVM, arteriovenous malformation.

Table 2 Goals of Superselective Angiographic Evaluation of Brain AVMs

1. Distal feeding pedicles (anatomy, aneurysms, geometry, hemodynamics)
2. Arterionidal junction
3. Nidus (compartments, direct AV fistulas, plexiform regions, intranidal ectasias, and aneurysms)
4. Venonidal junction
5. Proximal aspects of the draining veins
Abbreviations: AVM, arteriovenous malformation; AV, arteriovenous.

Source: From Ref. 114.

(B) Classification of Brain AVMs

Brain AVMs are categorized into ***superficial*** (cortical) or ***deep*** types. Cortical AVMs are subcategorized into sulcal, gyral, and mixed (sulcogyral) types. Deep AVMs are subdivided into subarachnoid, deep parenchymal, plexal, and mixed types (38).

A sulcal AVM nidus occupies the subpial space of the sulcus. The nidus may remain contained within the sulcus or variably extend through the sulcus into the cerebral cortex, into the subcortical white matter,and into the deep white matter to the ventricular wall.

Sulcal AVMs assume a conical or pyramidal shape conforming to the sulcal space. Their most superficial aspect is covered by the meninges, not by parenchyma. Because of this, meningeal arterial supply to their superficial aspect is common. Pial arteries are their primary supply. These end in the nidus after providing cortical and medullary branches to

adjacent gyri (terminal feeders). This terminal supply is usually amenable to safe embolization. Larger sulcal AVMs also receive supply from basal perforating arteries (38).

Gyral AVMs are covered by cortex and are typically spherical. The gyrus usually is enlarged and adjacent sulci are compressed. A large gyral AVM may extend into the subcortical white matter toward the ventricular wall. The arterial supply is primarily from pial branches that continue beyond the AVM to supply normal parenchyma (indirect feeders). Meningeal supply typically is absent because the overlying cortex is positioned between the nidus and the meninges. Basal perforating arteries may supply the deeper extension of a large gyral AVM (38).

Mixed (sulcogyral) types usually are large AVMs that combine both sulcal and gyral features. The AVM typically involves gyri and sulci, extending into the subcortical white matter to the ventricular wall. The arterial supply combines meningeal arteries and ter-

minal pial branches from the sulcal component, non-terminal pial branches from the gyral component, and basal perforating arteries (38).

Deep AVMs are relatively rare. They can be subdivided into subarachnoid, deep parenchymal, plexal, and mixed types. Subarachnoid AVMs are found in the basal cisterns and fissures, supplied by the subarachnoid portions of the choroidal and perforating arteries. Deep parenchymal AVMs are located in deep gray and white matter such as the thalamus, basal ganglia, and corpus callosum. Basal perforators, choroidal arteries, basal circumferential arteries, and medullary pial branches supply them. Plexal AVMs are intraventricular, primarily supplied by the choroidal arteries. Mixed deep AVMs are typically larger, combining subarachnoid, deep parenchymal, and plexal features. Venous drainage is predominately into the deep venous system; however, transmedullary cortical venous drainage also is seen (38).

(C) Angioarchitecture of Brain AVMs

The routine use of superselective angiography in addition to conventional selective cerebral angiography in recent years has added considerably to the understanding of brain AVM angioarchitecture.

1. Feeding Arteries

The classification of the arterial feeders to a brain AVM using *anatomic, geometric, and hemodynamic* criteria is essential for planning and performing endovascular embolization.

Anatomically, pial supply may be provided by extracortical (subpial), cortical, medullary, and/or corticomedullary branches. Meningeal supply may be direct or through transdural pial anastamoses. Collateral supply can occur through leptomeningeal and subependymal anastamoses. Choroidal artery supply can arise from the extraventricular (fissural, parenchymal) or intraventricular portions (39,40).

Geometric classification of arterial feeders defines the relationship of the distal feeder with the nidus and normal parenchyma. Three types are defined on superselective angiography: terminal, pseudoterminal, and indirect (39,40). The terminal feeder ends within the nidus distal to branches supplying normal brain. Terminal feeders are usually large, facilitating their superselective catheterization.(39,40). The pseudoterminal feeder appears to end in the nidus, but actually continues beyond to supply normal brain. The distal segment is not angiographically visible because of the high flow (sump effect) into the nidus. Its presence must be inferred on an anatomic basis. Changing hemodynamic conditions during embolization of a pseudoterminal feeder can cause the embolic material to occlude the distal portion to normal brain, resulting in an ischemic complication (39,40). The indirect feeder (feeder en passage) is a branch to the nidus

arising from an artery that passes in proximity to the nidus while continuing on to supply normal brain. Indirect feeders are typically smaller and shorter, usually originating at an acute or right angle from the parent vessel. Superselective catheterization is often feasible, but more difficult. The parent vessel may be enlarged up to the origin of the indirect feeders and smaller beyond (39,40).

Hemodynamically, feeding arteries may be characterized into dominant or supplementary feeders according to the amount of flow Most cerebral AVMs contain a combination of both types of feeders (38).

High-flow angiopathy results in stenoses in the feeding arteries in up to 20% of brain AVMs. These may be isolated, proximal stenoses intrinsic to the vessel wall or rarely caused by extrinsic compression. Diffuse stenoses with a moyamoya appearance are occasionally seen in younger patients (40). Arterial stenoses associated with decreased distal tissue perfusion may result in a shift in the watershed zone toward the nidus (watershed transfer), occurring in up to 30% of superficial (cortical) AVMs. Cortical arteries and leptomeningeal collaterals are recruited to supply more of the territory distal to the AVM. This shift in arterial supply may perfuse just the normal parenchyma or also include the distal aspect of the AVM nidus. Angiogenesis can occur with watershed transfer in response to chronic parenchymal ischemia. It may be mistaken for part of the nidus; however, angiogenesis has no AV shunting and is not a true AVM component (40).

2. AVM Nidus

The nidus is considered the region between very distal aspects of the readily identifiable arterial feeders and the proximal aspects of the draining veins. AV shunting occurs at this site and represents the primary target of embolization. Complete obliteration of the

nidus results in a cure (39,40). Most brain AVMs have a ***compact,*** well-defined nidus with well-demarcated borders, discrete feeding arteries, and draining veins. A minority has ***diffuse*** and ill-defined margins. Angiogenesis associated with watershed transfer may mimic a diffuse nidus.

Nidal ***sizes*** vary tremendously. Yasargil classified them into micro AVMs (< 1cm), small (1-2), Moderate (2-4cm) , Large (4-6cm) and Giant (> 6cm) (ref b) Their ***shapes*** tend to conform to their anatomic environments. Sulcal AVMs are usually conical, gyral and subcortical white matter AVMs tend to be spherical , and deep AVM shapes vary with location (callosal, cisternal, etc.). Larger AVMs have more complex shapes reflecting their involvement with multiple anatomic structures (38).

Superselective angiography has led to the concept of the nidal ***vascular compartment***, referring to an intranidal vascular unit consisting of one or more feeding arteries supplying the region of AV shunting with a unique draining vein. A nidus may be composed of one or multiple vascular compartments of varying sizes and flow patterns. The AV connections within a given compartment may be plexiform, fistulous, or mixed. These compartments are often hemodynamically interconnected, so occlusion of the compartmental feeders without occlusion of the compartmental zone of AV shunting may allow the compartment to continue to fill from neighboring units. Compartmental vein occlusion can increase the risk of nidal rupture. Hence, careful characterization of the compartmental angioarchitecture is essential for planning an embolization (38).

Histological studies have described the nidus as a complex system of coiling and intercommunicating vascular channels emptying into tortuous thin walled collecting veins. ***Three zones*** have been described within the nidus: arterial, intermediate, and venous. The ***arterial zone*** consists of a plexus of interconneing thick-walled vessels. The ***intermediate zone*** is

very heterogeneous, containing four types of coiled, interconnected channels ranging from 0.15 to 1.0 mm in diameter. ***The venous zone*** consists of 1- to 3-mm thin-walled vessels converging into the draining veins. AV shunting is thought to occur between the arterial and intermediate zones (41).

3. Draining Veins

The location of a brain AVM usually predicts the pattern of venous drainage; however, there are frequent variations. Cortical AVMs (sulcal and gyral) typically drain through cortical veins into the nearby dural sinuses. Those with subcortical or ventricular extension often have both *superficial* (cortical) and *deep* (subependymal) venous drainage. Central AVMs usually drain into the deep venous system. However, unexpected patterns, such as transcerebral cortical venous drainage of a deep AVM or deep venous drainage of a cortical AVM, may be seen approximately 30% of the time. These variants may represent venous collaterals that developed after occlusion of the original venous drainage system (40).

Important aspects of the nidal venous drainage include venous anatomic variations, collateral venous drainage, and high-flow angiopathy. Anatomic variations in venous drainage develop in response to hemodynamic effects, such as persistence of embryonic veins and variations in the cerebral veins and dural sinuses. Collateral venous drainage is acquired as a response to obstruction including ipsilateral, contralateral, and transcerebral rerouting of venous drainage. This may be due to mechanical venous compression or intrinsic venous stenoses or thromboses due to high-flow angiopathy. Insufficiently developed collateral venous drainage may result in venous hypertension, venous aneurysms, and venous ectasia (varix) proximal to the obstruction, especially in high-flow AVMs. Clinical symptoms may result from direct compression of the brain or cranial nerves by the varix,

seizures or neurological deficits from venous hypertension, and hemorrhage from AVM rupture (38,40).

4. Aneurysms Associated with Brain AVMs

(a) Introduction. The association of aneurysms with brain AVMs has been reported for many years although until recently little was known regarding the frequency or clinical implications of their concomitant occurrence. The publication of relatively large series has enabled study and understanding of some aspects of the association between these two cerebrovascular lesions. Although much remains to be understood, it is clear that significant clinical and therapeutic implications may arise from the relatively common association of these two cerebrovascular lesions.

(b) Classification. Classification of aneurysms associated with AVMs was first proposed by Hayashi et al. in 1981 (42). These authors included only aneurysms external to the AVM nidus in their classification. They divided extranidal aneurysms into three groups

depending on whether they were located proximally or distally on vessels giving supply to the AVM or were located on vessels unrelated to the AVM supply.

In 1994, the Tew's classification (Table 3) divided AVM-associated aneurysms into four groups based on their relationship to the AVM nidus and feeding arteries (43). This classification also includes intranidal aneurysms (Type IV). This comprehensive and relatively straightforward classification has the advantage of suggesting potential mechanisms for aneurysm formation based on location. In addition, it has proven useful in attempts to relate aneurysm types to clinical behavior.

Differences in definitions are often seen, however, with some series simplifying the classification into three or even two groups of aneurysms.

These often overlap and have included aneurysms unrelated to the AVM supply; flow-related aneurysms, which
have been subdivided into those located either proximally or distally on arteries supplying the AVM; and intranidal aneurysms (44–46).
Nevertheless, definitions of AVM-associated aneurysms similar to those outlined in the

Table 3 Tew's Classification of AVM-Associated Aneurysms

Type I Dysplastic or remote, not related to AVM supply
Type II Proximal, arising from the circle of Willis or origin of a vessel supplying the AVM
Type III Pedicular, arising from the midcourse of a feeding pedicle
Type IV Intranidal, within the AVM nidus
Abbreviation: AVM, arteriovenous malformation.

Source: From Ref. 43.

Tew's classification have become relatively standardized with publication of ''Reporting Terminology for Brain Arteriovenous Malformation Clinical and Radiographic Features for use in Clinical Trials'' (47).

(C) Epidemiology. The reported prevalence of aneurysms associated with AVMs varies widely among series. In an early examination of the subject, the First Cooperative Study of Intracranial Aneurysms and Subarachnoid Hemorrhage found intracranial aneurysms associated with 6.2% of 545 AVMs (48). Similarly, in a large series of 600 AVMs, Thompson et al. identified 7.5% patients whose AVMs were associated with extranidal aneurysms (49). Other series have noted prevalence of extranidal

aneurysms as high as 17.6% (50). In 1994, Turjman et al., using superselective angiography, demonstrated a considerably higher prevalence, which included a group of aneurysms located within the angiographic boundaries of the AVM nidus and which filled prior to filling of significant portions of the nidus. These intranidal aneurysms were identified in 58% of 100 consecutive AVMs (51). Meisel et al. evaluated 662 AVM patients and identified 46% with associated aneurysms. Among 305 patients having both aneurysms and AVMs, 372 of the aneurysms were identified as intranidal, with 313 located on vessels supplying the AVM (46). Halim et al. evaluated 336 AVM patients, 82 from University of California at San Francisco (UCSF) and 254 from Columbia Presbyterian Medical Center (CPMC). Their evaluation also included intranidal as well as extranidal aneurysm types. They found similar overall aneurysm prevalence at both institutions with 34% in the UCSF patients and 29% from patients evaluated at CPMC (45). Redekop et al., however, found a somewhat lower frequency and identified aneurysms in association with 16.7% of 632 AVMs of which 5.5% were intranidal aneurysms (52).

Overall, the reported prevalence of AVM- associated aneurysms falls generally into the range of 15% to 25%. Nevertheless, prevalence in individual series varies 10-fold, from 5.8% to 58% in different series. This variability in reported aneurysm prevalence may arise from a number of factors. These include poor interobserver agreement as to what constitutes an AVM-associated aneurysm, particularly aneurysms within or in proximity to the AVM nidus.

In addition, differing definitions, data collection methodology, and inclusion criteria, all impact on the diagnosis and classification of AVM-associated aneurysms. For example, whether aneurysms located within the AVM nidus are included can be expected to impact the overall numbers of aneurysms identified. Lastly, heterogeneity of study populations,

including referral bias, contributes to the variable prevalence reported in the literature.

Most series indicate that AVM-associated aneurysm prevalence is similar in men and women. The frequency of AVM-associated aneurysms has been noted, however, to increase with patient age, as well as flow rate and size of the AVM nidus.

Reported multiplicity of AVM-associated aneurysms is common but also quite variable. Ezura et al.,for example, found multiple aneurysms in 18 of the 25 patients (72%) to be AVM-associated aneurysms in their series, while Meisel et al. found 67% of their AVM-associated aneurysm cases to have multiple aneurysms (46,53,54). Data suggest that close to half of patients with AVM-associated aneurysms will have more than one aneurysm, and a significant proportion will have more than two aneurysms.

(d) Pathogenesis of AVM-associated aneurysms. Three major theories have addressed the association of AVMs and aneurysms. These include incidental occurrence, an underlying congenital vascular defect responsible for both lesions, and the flow-related or hyperdynamic theory.

Early suggestions were that the relationship between the two lesions was one of simple chance occurrence. However, most studies report a considerably higher frequency of aneurysms occurring in association with AVMs than would be expected by chance, and this theory is currently given little credence.

To date, no underlying congenital defect has been identified to explain an association between aneurysms and AVMs. While a number of genes have been found to be differentially expressed in AVM-feeding pedicles compared with normal cerebral vessels, current information suggests that this differential expression is likely a consequence of increased flow dynamics rather than an underlying cause of the AVM (55). A number of

other heritable disorders, many of which involve defects in connective tissue, have also been associated with an increased prevalence of intracranial aneur-ysms (57). No convincing evidence has been presented to suggest an increase in brain AVMs associated with any of these conditions.

Flow phenomena associated with the AVM provide a logical mechanism to explain the greater than expected prevalence of aneurysms on AVM feeding vessels. This theory, initially articulated by McKissock over 50 years ago, bases the development of aneurysms on the hyperdynamic flow resulting from AV shunt through the AVM (58). The low resistance through the AVM and consequent increased velocity in feeding arteries places increased shear stress on the vessel walls. While aneurysm formation is undoubtedly multifactorial, abnormal shear stress acting on the arterial wall has been found to play a role in formation, growth, and rupture of all types of arterial aneurysms (59–61). Indeed, no histological or imaging features have been found to distinguish flow-related aneurysms occurring in association with AVMs from those aneurysms occurring in the absence of AVMs.

Support for a hyperdynamic flow mechanism comes from the observed tendency of aneurysms to arise far more commonly on vessels providing arterial supply to the AVM, than on unrelated vessels. An analysis of 78 reported cases of AVM-associated aneurysms, by Okamoto et al., showed a significant correlation of aneurysm location to vessels supplying the AVMs (62). This was reinforced by the results reported by Cunha e Sa et al. who found 98% of AVM-associated extranidal aneurysms on vessels directly supplying the AVMs (63). In addition, Redekop et al. identified flow related aneurysms in 11.2% of 632 AVMs, while aneurysms on vessels unrelated to the AVM were found in

only 0.8% (52). These authors also found a tendency for aneurysms to occur more often on arteries feeding larger AVMs, and therefore associated with higher flow, than on arteries supplying smaller AVMs.

Additional support for a hyperdynamic flow mechanism underlying many AVM-related aneurysms arises from frequently observed changes in aneurysm size following treatment of the AVM and consequent decrease in the AV shunt. Examination of 23 proximal aneurysms following complete AVM obliteration revealed disappearance of one (4.3%) and a decrease in size of four (17.4%) aneurysms. In the same patient population, four (80%) of five distally located aneurysms regressed completely and one was unchanged (52). These data emphasize the effect of AVM flow on changes in aneurysms located along feeding arteries. They also suggest that more distally located aneurysms are more sensitive to alterations in flow than those located more proximally.

Additional controversy surrounds the etiology of *intranidal* aneurysms. Many believe that these lesions represent true aneurysms located in the most distal arterial branches adjacent to the AVM nidus. Other authors have suggested, however, that some of these lesions represent early filling of dilated venous pouches rather than true arterial aneurysms, while others may represent pseudoaneurysms arising as residua of prior hemorrhages (64).

Clinical implications. The natural history of AVMs associated with aneurysms has been the subject of considerable controversy. Some data suggest that increased rates of both initial and recurrent hemorrhage occur in patients who have AVMs with concomitant aneurysms. Piotin et al. found that 50% of their patients with AVM-associated aneurysm presented with intracranial hemorrhage. Of these, 80% had bled from their aneurysms (65). Similarly, Batjer et al. found that for patients who

harbored both lesions and presented with intracranial hemorrhage, 78% had bled from the associated aneurysms(66). Cunha e Sa et al. identified the source of intracranial hemorrhage in patients with AVM-associated aneurysms as the aneurysm in 46% of their series (63).

Brown et al. emphasized the long-term risk of harboring an aneurysm in association with an AVM. They found that patients with AVM-associated aneurysms had an annual hemorrhage risk of 7% at five years following diagnosis. This was significantly higher than the1.7%annual hemorrhage rate for those AVM patients without coexisting aneurysms (50).

Studies of clinical behavior also suggest that important differences may characterize different types of AVM-associated aneurysms. Intranidal aneurysms have been associated with a higher incidence of initial hemorrhage as well as with multiple episodes of recurrent bleeding. For example, Redekop et al. noted intracranial hemorrhage associated with 38% of their series of 632 AVMs. Presentation with intracranial hemorrhage occurred in 72% of patients with intranidal aneurysm; 36% without aneurysm; and 40% with flow-related or unrelated aneurysms. These authors also found an annual hemorrhage rate of nearly 10% among patients with intranidal aneurysms who were not treated (52).

Despite the difficulty in formulating risk profiles ssociated with AVM-associated aneurysms in genral, aneurysms seem to present more of a risk of hemorrhage when located closer to or within the AVM nidus. Given this information, a number of management approaches to patients identified as having AVM-associated aneurysms have been suggested.

(e) Treatment approaches. Specific management recommendations for patients having both aneurysm(s) and an AVM are difficult to formulate because of the relatively sparse and often conflicting data. General guidelines have been suggested, however. For patients presenting with hemorrhage, the first step is to determine which lesion was responsible for

the hemorrhage. It is that lesion toward which the initial treatment should be directed. When no determination can be made as to the source of hemorrhage, the greater morbidity and higher chance of repeat hemorrhage from an aneurysm dictates that the aneurysm be addressed as a first priority. In cases where the AVM is identified as the source of hemorrhage, initial treatment is directed at that lesion. Most data indicate that intranidal aneurysms associated with AVMs presenting with hemorrhage should be strongly considered to be the source of hemorrhage and treatment initially directed at this feature of the AVM (46). The specific treatment depends on the overall treatment plan for the AVM. resection If performed, endovascular treatment should be targeted to close the feeding pedicle from which the aneurysm originates first in order to minimize the chance of subsequent hemorrhage.

Differing recommendations have been made with respect to prophylactic treatment of feeding artery aneurysms in conjunction with AVM hemorrhage (ie in cases of unbled aneurysms/AVMs).Thompson et al. found that of 45 aneurysms identified in their 600 patients (7.5%), five bled prior to treatment while two bled within three weeks following AVM treatment. Their experience led them to recommend treatment of aneurysms on feeding vessels prior to definitive treatment of the AVM (49). Similarly, Ezura et al. treated feeding artery aneurysms endovascularly prior to treating the AVM with either resection or radiosurgery (53). However, others suggest that decreasing flow through the AVM results in frequent regression of extranidal aneurysms without the need for direct treatment. For example, Redekop et al. reported complete spontaneous regression of aneurysms on distal feeding arteries in 80% of cases after curative therapy of the AVM (52). These authors also noted shrinkage of proximally located aneurysms in 18% of cases with complete disappearance in 4%. The effect on aneurysms appeared to be

less in cases of incomplete AVM treatment. Of 16 patients with less than 50% reduction in the AVM, no aneurysms regressed, although two enlarged and bled. In cases with greater than 50% reduction in the AVM, two of three distal aneurysms disappeared and five proximal aneurysms were unchanged. Meisel et al. also reported significant regression of feeding artery aneurysms after treatment of the AVM (46).

(f) Summary. Aneurysms are found in association with a significant proportion of AVMs. They may occur within the AVM nidus, on routes of flow to the AVM, or on vessels unrelated to the AVM supply. In any case, AVM-associated aneurysms represent an additional source of potential morbidity that must be considered in formulating treatment of the AVM patient.

ANGIOGRAPHIC GRADING SYSTEMS FOR BRAIN AVMs

Because of the tremendous variability of brain AVMs with respect to their anatomy and biological behavior, a number of studies have attempted to correlate specific criteria of AVM characteristics with therapeutic outcomes to guide clinical decision-making. Most
of these grading systems have focused on surgical management. Luessenhop and Gennarelli were the first to assign a grade to a brain AVM in an effort to predict operability and outcome. Grading was based on the number of arteries feeding the AVM and the vascular territory that was involved. Other criteria such as size, anatomic location, degree of vascular steal, and venous drainage were not included, limiting the system's utility (70).

In 1986, two new grading systems were proposed. Shi and Chen categorized AVMs on the basis of four criteria: (1) size, (2) location and

depth, (3) complexity of the arterial supply, and (4) complexity of the venous drainage. Each criterion was attributed a grade of I to IV on the basis of a detailed analysis that was related to the operative risk. A composite grade was assigned on the basis of the grades for the individual criteria. This complex system did not gain widespread usage (71).

Spetzler and Martin also proposed a grading system for brain AVMs in 1986 that has become the most widely utilized. The authors sought a system that was simple and applicable to all brain AVMs providing a reasonable estimate of operative morbid

ity and mortality. They considered a number of parameters, including the AVM size, the number of feeding arteries, the anatomic location, the operative accessibility, the amount of flow, degree of vascular steal, the eloquence of nearby brain parenchyma, and the venous drainage pattern (72).

Recognizing that a grading system that attempted to incorporate all of the potential parameters would be too complex to be practical, and that many of those variables were interrelated, they proposed a simplified grading system based on three criteria: the AVM size,the venous drainage pattern, and the eloquence of the adjacent brain parenchyma. The AVM size was divided into three categories: small (<3 cm), medium (3 to 6 cm), and large (>6 cm). The venous drainage was designated as superficial only if all of the venous drainage emptied into the cortical venous system. If any or all of the venous drainage egressed through deep veins (internal cerebral, basal veins, precentral cerebellar vein) it was categorized as deep. An AVM was considered to be adjacent to eloquent brain parenchyma if it was next to the sensorimotor cortex, language areas, visual cortex, hypothalamus, thalamus, internal capsule, brain stem, cerebellar peduncles, or deep cerebellar nuclei (72).

When using the Spetzler-Martin grading system, points are assigned for the AVM size, the venous drainage pattern, and the location relative to eloquent brain (Table 6). The points for each parameter are added for the total score (1–5) that corresponds to the Spetzler-Martin grade (I–V). For example, a 2-cm anterior frontal lobe AVM with cortical venous drainage (1 point for size, 0 points for venous drainage, 0 points for eloquence) is a Spetzler-Martin grade I AVM, whereas a 4-cm thalamic AVM with deep venous drainage (2 points for size, 1 point for venous drainage, 1 point for eloquence) is a Spetzler-Martin grade IV AVM. AVMs with no possibility of surgical resection (e.g., diffuse brain stem or holohemispheric involvement) are assigned a grade of VI (72).

Following resection of Spetzler-Martin grade I and II AVMs, the authors' retrospective evaluation of their personal surgical experience found a low incidence of minor deficits (0%, 5% in grade I AND II, respectively) and no major neurological deficits; grade IV and V AVM resections were associated with signif-icant incidences of both minor deficits (20%, 19% in grade IV and grade V, respectively) and major deficits (7%, 12% in grade IV and grade V, respectively) (72).

A subsequent prospective evaluation confirmed the accuracy of the Spetzler-Martin grading system for predicting both new-temporary and new-permanent neurological deficits (73). A recent analysis demonstrated interobserver variability between a neuroradiologist and a neurosurgeon performing Spetzler- Martin grading in 27.7% of patients; however, this variability did not diminish the predictive value of the Spetzler-Martin scale (74).

Table 6 Spetzler-Martin grading system for brain AVMs

AVM Feature	Points
Size of nidus	
<3 cm (small)	1
3–6 cm (medium)	2
>6 cm (large)	3
Eloquence of adjacent brain	
Noneloquent	0
Eloquent	1
Venous drainage	
Superficial	0
Deep	1

The assigned grade equals the sum of the points for all the three features.

Abbreviation: AVM, arteriovenous malformation.

Source: From Ref. 72.

EMBOLIZATION OF BRAIN AVMs

(A) Historical Background

In a landmark publication in 1960, Luessenhop and Spence reported the first therapeutic embolization of a brain AVM (75). Because this report predated the development of selective cerebral angiography, the authors injected Silastic spheres directly into a surgically accessed cervical internal carotid artery. Their technique relied on the much greater rate of blood flow to the AVM to direct the spheres into the nidus rather than into normal cerebral branches; however, this flow-dependent embolization was unreliable and

was associated with a significant risk of causing an ischemic infarct. Another problem was that the relatively large spheres lodged in the proximal feeders and did not penetrate into the nidus. The nidus remained unoccluded and could recruit deep perforating arteries that were much more difficult to control during surgery (76–79).

In 1974, Serbinenko was the first to report superselective cerebral artery catheterization and embolization using a detachable balloon attached to a flexible, flow-directed catheter (80). Superselective catheterization of the target vessel with the balloon catheter was

not always technically feasible because it depended on the arterial geometry and hemodynamics. Similar to the problem with the flow-directed Silastic spheres, the detachable balloons occluded the proximal arterial feeders inducing the nidus to recruit new blood supply from other branches that were often more difficult to control during surgery. This

early experience suggested the AVM nidus should be the target of therapeutic embolization.

In 1976, Kerber set the stage for the development of modern therapeutic brain AVM embolization techniques. He reported the use of a microcatheter with a calibrated-leak balloon to superselectively catheterize cerebral arteries and to deliver a liquid embolic agent [isobutyl-2-cyanoacrylate (IBCA)] into the AVM nidus (81). However, both the catheter and the embolic agent had serious limitations. Calibrated-leak balloon catheters were difficult to use and were associated with multiple complications including vascular injuries. The catheters also could be permanently glued into the AVM (82). In addition, the IBCA transformed the AVM into a hard, incompressible mass with ill-defined borders and containing embolized vessels that were difficult to surgically cut or coagulate (82,83). IBCA also was reported to be carcinogenic and associated with toxic reactions (84,85).

These pioneering efforts provided the foundation and stimulus for the development of the microcatheters, guidewires, and embolic agents that are currently used for AVM embolization. This early experience also established the concept of targeting the nidus for embolic occlusion, and defined the risks of embolizing too proximally (the arterial feeders) and too distally (the venous outflow).

(B) Embolization Indications

Current therapeutic options for brain AVMs include embolization, microvascular surgery, stereotactic radiation (radiosurgery), and various combinations. The goal of any combined therapy is to decrease the overall morbidity and mortality of AVM treatment. In many centers, brain AVM embolization is most commonly performed before microsurgical resection.

Embolization is also performed prior to radiosurgery. In this setting, the goal is to permanently occlude enough of the nidus so that stereotactic radiation can target the rest with a higher dose and a better chance for cure. Less frequently, embolization is used as a stand-alone curative technique, especially for small, surgically difficult lesions. Occasionally, embolization is employed for the palliation of symptoms from an otherwise untreatable AVM. Ideally, a multidisciplinary team consisting of a microvascular neurosurgeon, an interventional neuroradiologist, and a radiation therapist collectively evaluates and formulates an individualized plan for each patient.

(i) Presurgical Embolization

Microvascular surgery has been the oldest and still principle method to treat brain AVMs at many centers. Neurosurgical outcomes have improved with advances in stereotactic guidance, electrophysiological monitoring, barbiturate anesthesia, intraoperative angiography, and aggressive perioperative blood pressure control. Many small, superficial brain AVMs can be surgically resected without preoperative embolization with minimal mor-bidity and mortality (73). Nonetheless, preoperative embolization results in improvements in overall treatment outcomes for many brain AVMs.

Brain AVM embolization can improve surgical outcomes through several mechanisms. Often, the most valuable contribution is the elimination of deep or surgically inaccessible feeders. Preoperative embolization of the deep arterial supply can allow an otherwise inoperable AVM to be successfully resected (86). Also, embolization can decrease the size of the nidus and the amount of blood flow through the AVM resulting in shorter surgical times and less blood loss. Embolized vessels also are easily identified during surgery. Finally, preoperative embolization of feeding

vessel and nidal aneurysms can eliminate those angioarchitectural risk factors for perioperative hemorrhage.

Proximal feeding artery aneurysms are at risk for rupture after AVM resection because elimination of the AV shunt causes a sudden increase in arterial pressure. These proximal aneurysms may be impossible to access through the craniotomy for the AVM resection, and preoperative embolization eliminates the need for a second craniotomy (86,87).

There is a general consensus that many superficial Spetzler-Martin grade I and II AVMs can be surgically resected with minimal morbidity and mortality without preoperative embolization. In these cases, the additional risks of embolization may not be justified. There are, however, exceptions such as a grade I or II AVM with a deep feeder that is difficult to access surgically (88,89). Also, some experts advocate embolizing an intranidal aneurysm in a Spetzler- Martin grade I or II AVM presenting with acute hemorrhage to stabilize the nidus until surgery (89). Embolization is used frequently for Spetzler-Martin grade III AVMs, particularly for those in central and eloquent locations and those with deep feeders. Pre-operative embolization (often staged) is commonly employed for those Spetzler-Martin grades IV and V AVMs considered for resection.

(ii) Preradiosurgical Embolization

There is a wide variability at different institutions in the use of combined embolization and radiosurgery. Stereotactic radiosurgery primarily is employed at some centers for small brain AVMs that have a high surgical risk because they are deep-seated or are located in the eloquent cortex. Other centers frequently use embolization to render large brain AVMs amenable to stereotactic radiosurgery. In this setting, embolization is used to reduce the size of the AVM to increase the probability of a radiosurgical cure (90). The rate of cure after stereotactic radiosurgery significantly

decreases as the volume of AVM being treated increases (91–93). Radiosurgical cure is more likely after embolization has reduced the residual AVM volume to less than 10 cc (90,94). Embolization is also performed prior to radiosurgery to occlude nidal aneurysms that represent a risk for hemorrhage until the radiosurgically induced obliteration occurs and also to occlude high-flow fistulas that may be refractory to radiosurgery (90). Repeat embolization or surgery also can be used to treat residual AVM persisting after radiosurgery (96,97).

(iii) Curative Embolization

There is currently a limited role for curative embolization of brain AVMs. Although embolization can successfully obliterate some small AVMs that have limited feeders, it rarely cures large, complex AVMs. Most of the AVMs that have a relatively high probability of cure with embolization are amenable to complete surgical removal with negligible morbidity and mortality. Therefore, justifying the risks of an attempted curative embolization is often questionable (73,98). Small deep central AVMs with limited feeders are exceptions where curative embolization can play an important role (99).

However, in carefully selected cases with small nidus and good vascular access restricted to one or few feeders, a curative goal may be attained. In our series, out of 78 patients, 15 (19%) patients had curative total obliteration of the nidus.

(iv) Palliative Embolization

Palliative embolization does not appear to improve on conservative medical management of most patients with incurable AVMs and may even worsen the subsequent clinical course (100). There are, however, appropriate goal-directed roles for palliative embolization in select

circumstances. Palliative embolization can alleviate symptoms due to vascular steal and mechanical compression and obliterate specific aneurysms responsible for repeated hemorrhages. Embolization of meningeal supply can improve intractable headaches (101–103).

(C) Embolization Tools and Technique

(i) Microcatheters and Guidewires

The flow-directed microcatheters currently used for embolization with liquid agents are designed for safe and reliable navigation into the very distal aspects of the intracranial circulation. They have several segments of progressive softness. The proximal segments

are relatively stiff and thick-walled to transmit longitudinal motion and torque efficiently. The transitional middle segments have thinner walls and progressively increase in flexibility but remain ‘‘pushable.’’ The distal segments are small (1.3 to 1.8 F outer diameter), thin walled, and extremely soft and supple. They provide no intrinsic transmission of longitudinal force. The catheter tips are slightly bulbous so blood flow will pull them forward. The microcatheters have hydrophilic surface coatings to decrease thrombogenicity, facilitate movement through small tortuous vessels, and prevent adhesion of embolic agents. Recently introduced ‘Sonic’ microcatheter has a detachable tip provided with an aim of allowing sustained and prolonged onyx injection.

Guidewires designed for use in the cerebral arteries (0.007–0.014 inch) have very flexible distal segments and soft, shapeable platinum tips. They also are covered with a hydrophilic coating to reduce friction between the catheter and guidewire. They remain ‘‘torquable’’ even after they have gone through several curves. Only the smallest guidewires, such as the

0.008-inch Mirage (EV3, Plymouth, Minnesota, U.S.), will pass through the flow-directed microcatheters commonly used with liquid embolic agents (104).

(ii) Vessel Selection

Current techniques for brain AVM embolization require advancing a suitable microcatheter into the very distal aspect of an arterial feeder supplying the nidus. A guide catheter (e.g., Envoy, Cordis Endovascular, Miami Lakes, Florida, U.S. or Vista Brite) first is placed in the distal cervical aspect of the appropriate internal carotid or vertebral artery. A 6-Fr guide catheter is preferred for easier contrast injections while the microcatheter is inserted; however, a 5-Fr guide catheter may be safer in a small vertebral artery. A rotating hemostatic valve is used for coaxial placement of a microcatheter and to continuously flush the guide catheter with heparinized saline. Intravenous heparin is administered on an individual basis to prevent thromboemboli if there are small feeders or there is slow flow. A microcatheter (1.5- or 1.8-Fr Spinnaker Elite, Boston Scientific Corporation, Natick, Massachusetts, U.S.; Marathon or Ultraflow, EV3) with a small steam-shaped distal curve (e.g., 1-mm radius distal ‘‘J’’ shape) is navigated through the cerebral arteries under continuous subtracted fluoroscopic (road-map) imaging. There are two primary techniques for intracranial navigation: flow directed and guidewire assisted. Flow-directed navigation uses arterial blood flow to drag the very flexible distal catheter segment and slightly bulbous catheter tip forward. The tip will preferentially tend to advance into the vessel with the highest flow, which is usually the desired feeder to the AVM. Directional control also is facilitated by gentle injections of contrast to redirect the curved tip into the desired branch. For guidewire-assisted navigation, a 0.008-inch

Mirage (EV3) guidewire is advanced into the distal segment of the microcatheter to augment its ‘‘pushability’’ and to change shape of the catheter tip. Advancing and withdrawing the guidewire in the distal segment also changes its elasticity often prompting the catheter tip to spring forward. When necessary, the Mirage guidewire can be extended beyond the microcatheter tip to navigate difficult anatomy; however, this must be done with caution to avoid arterial perforation or dissection.

(iii) Embolic Agents

There are three general categories of currently available embolic agents: solid occlusive devices (coils, silk threads, balloons), particulates [polyvinyl alcohol (PVA) particles], and liquids (cyanoacrylates, Onyx, ethanol) (115). Solid occlusive devices primarily are used to occlude large direct AV fistulas. Particulate embolization using PVA particles has been replaced by liquid embolization with N-butyl cyanoacrylate (NBCA) at most centers (109). Onyx is a new liquid embolic agent recently approved by the Food and Drug Administration (FDA) (116). Although absolute ethanol and silk threads have been used to embolize brain AVMs, limited results have been published (117,118).

(aa) Polyvinyl alcohol particles. PVA particles were commonly used for brain AVM embolization before liquid agents such as NBCA and Onyx became more widely used. PVA particles are supplied in various size ranges from 50 to 1000 mm. They are nonradiopaque and are mixed with iodinated contrast for delivery. PVA particles were often used in combination with coils or silk threads to facilitate their retention, especially in larger AV shunts (119). Typically, larger (e.g., 3-Fr) over-the-wire microcatheters have been required for larger PVA particles (>500 mm) resulting in more proximal embolizations of the arterial feeders srather than the nidus (89).

PVA particles have several disadvantages ascompared to liquid embolic agents. They can occlude the small, flow-directed microcatheters that can bemost reliably advanced into the distal feeder. Also,since the particles are radiolucent, it is not possible to identify where they deposit. There is evidence they often aggregate and frequently occlude the arterialfeeder rather than the nidus. The nidus can then recruit collateral blood supply and regrow. This may explain why Sorimachi et al. found 43% of brain AVMs partially embolized with PVA particles demonstrated an increase in the size of the nidus on follow-up angiograms (119). In addition, a histopathological analysis revealed PVA embolized vessel lumens contained clumps of particles intermixed with thrombus rather than solid luminal packing with PVA. Eighteen percent of the embolized vessels were partially recanalized (120). This may explain why AVMs that appear completely obliterated on angiography after PVA embolization can reappear on follow-upexams (119). This conclusion is supported by the observation that 15% to 20% of AVM patients undergoing PVA embolization prior to radiosurgery had recanalization two to three years later on follow-up angiography (92,94).

(ab) N-Butyl cyanoacrylate. Cyanoacrylates have been used for brain AVM embolization for more than 20 years. Early problems with cyanoacrylate embolization that prevented wide-spread use have been solved with the replacement of previous formulations with NBCA and with advances in microcatheter and guidewire technology (109). The FDA approved NBCA (Trufill, Cordis endovascular)for brain AVM embolization in 2000. NBCA has been the most commonly used embolic agent for this purpose in the United States before the advent of Onyx. The Cordis NBCA kit contains NBCA, ethiodol, and tantalum powder. Ethiodol is mixed with NBCA to prolong the polymerization time and also

to make the solution radiopaque. Tantalum power can be added to the NBCA/ethiodol mixture to further increase its radiopacity. The liquid NBCA monomer undergoes a rapid exothermic polymerization catalyzed by nucleophiles found in blood and on the vascular endothelium to form an adhesive, non-biodegradable solid. The vessel is permanently occluded when the polymer completely fills the lumen. NBCA provokes an inflammatory response in the wall of the vessel and surrounding tissue leading to vessel necrosis and fibrous ingrowth. These histological responses also may contribute to the permanency of NBCA occlusions (121,122).

NBCA has a number of useful properties for brain AVM embolization. The liquid monomer can be injected through small (1.5 and 1.8-Fr) flow - directed microcatheters such as the Spinnaker Elite (Boston Scientific) and the Ultraflow (EV3) that can be reliably and safely positioned in the distal arterial feeder or within the nidus. This distal catheter positioning maximizes the likelihood of adequate nidal penetration to achieve a permanent occlusion and minimizes the risk of inadvertent embolization of normal branches (109).

The NBCA polymerization rate can be adjusted to satisfy specific requirements. The goal of the embolization is to form a solid intranidal NBCA cast, avoiding early polymerization in the arterial feeder or late polymerization in the venous outflow. Pure NBCA polymerizes almost instantaneously at the catheter tip. Although this may be necessary to occlude a direct high-flow fistula, immediate polymerization will not allow the NBCA to penetrate optimally into a plexiform nidus (109). The addition of ethiodol slows the polymerization rate, allowing better nidal penetration. The polymerization rate progressively decreases as more ethiodol is added. The objective is to use an ethiodol /NBCA mixture with

a polymerization time optimally matched to the individual AVM's angioarchitecture and hemodynamics.

The AV transit time on superselective angiography is subjectively evaluated as a guide to formulating the mixture. This is far from an exact science and is highly dependent on experience. The concept of a ''wedged'' catheter position, where forward flow is controlled by the rate of injection, theoretically allows slower, more controlled injections of a more dilute NBCA/ethiodol mixture with a longer polymerization time (109).

The use of ethiodol has *limitations*. A high ethiodol concentration also increases the viscosity of the mixture, which can conversely decrease the nidal penetration. Dilute NBCA mixtures also tend to disperse in small droplets that can incompletely cast the vessels, possibly allowing recanalization (122). Glacial acetic acid can be added as an alternative method to slow the rate of polymerization, without causing the increased viscosity of higher ethiodol/NBCA concentrations. This may result in better nidal penetration and more solid casting (123).

Many experts believe portions of the AVM nidus that are well cast with NBCA can be considered permanently obliterated (109). Wikholm followed 12 brain AVMs totally occluded with NBCA for 4 to 78 months and found no angiographic evidence of recanalization (124). In another study, six patients with complete obliteration of the AVM nidus had no angiographic evidence of recurrence at 17 to 32 months (125). NBCA embolization therefore has the potential to transform inoperable AVMs into surgically respectable lesions and to reduce the size of an AVM nidus sufficiently to make radiosurgery possible. Some small AVMs can be cured by embolization alone.A solid NBCA cast in the nidus is essential to assure permanent obliteration of the AVM (109).

Debrun described the single-column flow-controlled technique for optimal nidal filling using a microcatheter that is wedged intranidally and the use of a relatively dilute NBCA mixture (109). Solid casting is important since brain AVMs that were incompletely embolized with NBCA demonstrated histological evidence of capillary regrowth in the lumen of embolized vessels after three months (121).

Brain AVMs embolized with NBCA have favorable properties for surgical resection. The vessels are easily compressible and transected. The embolized feeders can be readily identified and differentiated from nonembolized en passage branches to normal brain. In addition, the embolization of the AVM nidus provides a distinct boundary zone between the AVM and normal brain (126).

NBCA Technique

The NBCA/ethiodol/tantalum mixture (Trufill, Cordis Endovascular) is prepared using clean gloves on a separate sterile table to prevent contamination with ionic catalysts. For a wedged injection (109), a relatively dilute concentration of NBCA (25–33%) is made by mixing 1 cc of NBCA with 2 or 3 cc of ethiodol in a shot glass. The vial of tantalum powder included in the Trufill kit is added to increase the radiopacity of the mixture. Relative hypotension is induced (20–30% decrease in mean arterial pressure).Test injections are made with a subtracted fluoroscopic image to confirm the catheter position and to gauge the optimal injection rate. The microcatheter is irrigated with 5% dextrose to flush all of the ionic catalysts from the lumen. The dilute NBCA solution is then injected slowly into the nidus over 15 to 60 seconds during continuous subtracted fluoroscopic observation. The injection rate is modified to obtain a solid nidal cast without causing proximal reflux. If a drop of NBCA enters a draining vein, the injection is paused several seconds. The injection is then

restarted if felt necessary with utmost care to avoid reflux into venous side.

The injection is also terminated if proximal reflux occurs. The microcatheter is aspirated and briskly removed. The guide catheter is aspirated and its tip is examined fluoroscopically. A postembolization angiogram is then obtained.

A nonwedged injection is performed in a similar fashion; however, a more concentrated NBCA solution is used because of the more rapid flow and the shorter arterial-venous transit time through the nidus. The injection rate is faster and the injection time is much shorter (one to three seconds). If a large direct fistula is present, maximal induced hypotension and a very high NBCA concentration are used. In this setting, coils (Liquid Coils, Target/Boston Scientific, Natick, Massachusetts, U.S.) can be injected first into the fistula to slow the rate of flow and to form a framework for the NBCA to adhere to, as was done in few cases in our series.

(ac) Onyx

Onyx (EV3) is a premixed, liquid embolic agent consisting of ethylene-vinyl alcohol copolymer (EVOH) and tantalum powder (for radiopacity) dissolved in dimethyl sulfoxide (DMSO). EVOH contains 48-mol/L ethylene and 52-mol/L vinyl alcohol (129). Taki et al. were the first to describe the use of EVOH, mixed with metrizimide powder (for radiopacity), dissolved in DMSO to embolize brain AVMs in 1990 (130). Subsequent studies led to a multicenter randomized trial that demonstrated noninferiority of Onyx compared to NBCA in achieving greater than or equal to 50% volume reduction for presurgical brain AVM embolization, resulting in FDA approval of Onyx for presurgical brain AVM embolization in 2005 (116,131,132).

Onyx is a cohesive, nonadhesive liquid embolic agent. The copolymer holds together as it is injected, but it does not adhere to the endothelium or to the microcatheter tip. When the mixture contacts an aqueous solution such as saline or blood, the DMSO diffuses away rapidly, causing the copolymer to precipitate into a soft, spongy solid. The precipitation progresses from the outer surface inward, forming a skin with a liquid center that continues to flow as the solidification continues. During the injection, the column of Onyx advances into the path of least resistance. The rate of precipitation of the copolymer is proportional to the concentration of EVOH in the solution. There are currently two commercially available concentrations of EVOH for brain AVM embolization: Onyx 18 (6% EVOH) and Onyx 34 (8% EVOH). Onyx 18 travels farther distally and penetrates more deeply into the nidus because of its lower viscosity and slower precipitation rate. Onyx 18 is used for distal feeding pedicle injections into a plexiform nidus, whereas Onyx 34 is recommended for embolizing high-flow fistulas. Complete solidification of both formulations occurs within five minutes.

DMSO was chosen as the solvent because it rapidly diffuses in aqueous solution and its physiological properties in humans are well known (130).DMSO is angiotoxic, however, with adverse effects that include vasospasm, angionecrosis, arterial thrombosis, and vascular rupture (133). These undesirable consequences are related to the volume of DMSO infused and the endothelial contact time (131). Severe angiotoxic effects do not occur when the DMSO infusion rate does not exceed 0.25 mL/90 sec (116,131).

Only specifically approved microcatheters (Ultraflow, Marathon, Echelon; EV3) can be used with Onyx because the DMSO will dissolve incompatibl catheters. Patients may notice a garlic-like taste for several hours, and their

skin and breath may have a characteristic odor due to the DMSO for one to two days after an embolization with Onyx.

The cohesive and nonadhesive properties of Onyx provide several advantages compared to NBCA. Because Onyx is nonadhesive and it solidifies more slowly than NBCA, typical injections are performed over much longer time intervals (minutes) and are easier to control. This procedure results in a much more leisurely embolization, providing time to analyze progress with interval angiography, if desired, and involving less risk of refluxing the embolic agent too proximally in the arterial feeders or extending too distally into the venous outflow . It is also possible that a more complete and solid casting of the nidus may be obtained with Onyx compared to NBCA. This may result in an increased rate of cure, but this remains to be proven. In addition, the catheter also can be repositioned into a second pedicle and another embolization can be performed, a maneuver that is not possible with NBCA. Finally, Onyx does not cause inadvertent gluing of the catheter tip to the vessel as fast as NBCA(116).

The available data on use of Onyx for brain AVM have been published and appears very encouraging. Jahan et al. embolized 23 brain AVMs achieving an average 63% reduction in AVM volume with 4% permanent morbidity and no mortality. Histopathological examination of the resected specimens showed mild inflammation one day after embolization and chronic inflammatory changes after four days. Angionecrosis was seen in two patients, but the vessel wall integrity was maintained in all specimens (116). In another study, the surgical handling characteristics of Onyx were compared with NBCA in embolized swine rete mirabile (132). Onyx was softer and handled better than NBCA during surgical resection. The permanency of Onyx embolization is as yet unknown. Short-term angiographic follow-up (1–100 days) did not reveal recanalization (116); however, no long follow-up studies have been published. Many other

hospital series have firmly established the safety and efficacy of Onyx - so much so that it has nearly replaced NBCA as agent of choice for AVM embolization.

Onyx Technique: Patients can experience pain during embolization with Onyx; therefore, general anesthesia is used more frequently than with NBCA. An Onyx compatible microcatheter is positioned in the desired location using flow-directed and guide-wire-assisted navigation as described above. Better nidal penetration is usually obtained in a larger feeder. A wedged intranidal position is optimal. After positioning of the microcatheter, a superselective angiogram is obtained. The Onyx solution must be vigorously shaken for 20 minutes to fully suspend the micronized tantalum powder. Mixing is continued until just before the embolization. Failure to do this may result in inadequate radiopacity (129). The manufacturer provides an adapted Vortex-Genie (Scientific Industries, Inc., Bohemia, New York, U.S.) to mix the Onyx. The catheter is flushed with normal saline and the dead space is loaded with pure DMSO solvent. The Onyx mixture is drawn into a DMSO-compatible 1-cc syringe, the syringe is connected to the microcatheter and a slow, steady injection is begun at a rate of 0.25 mL/90 sec to displace the DMSO in the dead space with Onyx. Subtracted fluoroscopy is begun just before the dead space volume has been replaced by the injection..

A slow, steady injection usually results in optimal nidal penetration. Changes in the injection rate tend to cause proximal reflux. The injection rate should not be allowed to exceed 0.25 mL/90 sec to prevent angiotoxicity. If proximal reflux occurs, the injection is paused 30 seconds and restarted. This allows a plug to solidify around the catheter tip that prevents further reflux and promotes forward flow. This ‘‘plug and push’’ technique can be repeated multiple times as required. Proximal reflux around the catheter tip should be

limited to 1 cm to avoid causing difficulty with the catheter retrieval. As a circumferential plug forms around the catheter tip, the injection can be paused for as long as two minutes to allow the plug to solidify. This will establish proximal flow arrest when the injection is restarted so that the subsequent flow will move distally. Similarly, if Onyx begins to fill a draining vein, a pause in the injection will allow that material to solidify, and when the injection is restarted the additional Onyx usually fills new areas of the nidus. The injection should never be paused for more than two minutes to prevent Onyx from precipitating in the catheter lumen. If there is resistance, the injection should be discontinued to avoid rupturing the catheter.

There are two *catheter retrieval techniques*. The slow ‘‘traction’’ method uses ncremental catheter withdrawal (cm by cm) with sustained moderate Tension on the catheter. The quick‘‘wrist-snap’’ technique is to withdraw the catheter enough (3–5 cm) to create slight tension and then quickly snapping the wrist (not the entire arm) 10 to 20 cm left to right.Pulling too far or hard runs the risk of causing a catheter separation.

Postprocedural Care

Patients are observed in the neurointensive care unit for 24 hours and usually discharged to home on the second postembolization day. Mild hypotension (mean arterial pressure ~90% of normal) may be induced for 24 hours if a large, high-flow AVM has been embolized. Additional embolization sessions for large, high-flow AVMs are staged every three to four weeks.

Results

The literature on outcomes for brain AVM treatments primarily consists of uncontrolled, single institution case series. Many of these have

demonstrated an important role for brain AVM embolization in selected patient populations. Nonetheless, they have relatively small sample sizes, and tremendous variability in selection criteria, techniques, patient evaluation, and follow-up. Multicenter, randomized, controlled outcome trials are needed to form a scientific basis for the selection of optimal therapeutic plans. Since brain AVM embolization is used mostly as an adjunct to surgery or radiosurgery, these trials will need to compare the natural history with the overall results of individual and combined treatment strategies.

Presurgical Embolization

A number of case series comparing groups undergoing surgical resection of brain AVMs with and without preoperative embolization have demonstrated that selective preoperative embolization improves overall outcomes (126,134,135). Preoperative embolization and surgery is also cost-effective compared to surgery without embolization, with cost per quality adjusted life-year savings as high as 34% (136).

Pasqualin et al. demonstrated that preoperative embolization of large, high-flow AVMs was associated with less intraoperative bleeding, and there were fewer postoperative neurological deficits, seizures, and deaths in the group that underwent preoperative embolization. The frequency of major new deficits was 31% in the surgery only group versus 5% in the combined embolization and surgery group. However, the incidence of postoperative hyperemic complications did not differ between the embolized and non-embolized groups (134).

Demeritt et al. compared 30 patients who underwent preoperative AVM embolization with NBCA followed by surgery with 41 patients who had surgery without preoperative embolization. The combined embolization and surgery group had a higher average Spetzler-Martin score compared to

the surgery only group (89% vs. 68% in grade III and IV, respectively) and a larger average nidal maximal diameter (4.2 1.5 cm vs. 3.4 1.8 cm); however, two-week and long-term Glasgow Outcome Scale scores were better in the combined embolization and surgery group than the surgery only group (70% vs. 41%, respectively, had a two-week Glasgow Outcome Scale score of 5; 86% vs. 66%, espectively, had a long-term Glasgow Outcome Scale score of 5) (135).

Similarly, Jafar et al. compared 20 patients who underwent preoperative AVM embolization with NBCA followed by surgery with 13 patients who had surgery alone. The combined group had a larger average AVM diameter (3.9 cm vs. 2.3 cm) and a higher average Spetzler-Martin grade (3.2 vs. 2.5) compared to the nonembolized group. Embolization complications included immediate and delayed hemorrhage (15%) and transient ischemia (5%). There was no embolization-related death. No difference in surgical complications was found between the embolized and nonembolized groups. The large majority of patients (91%) in both groups had good to excellent long-term neurological outcome. The authors concluded that ‘‘preoperative NBCA embolization of AVMs makes lesions of larger size and higher grade the surgical equivalent of lesions of smaller size and lower grade’’ (126).

Martin found that embolization was only effective to decrease blood loss and shorten operative time when the nidal size was decreased more than 66%. Less reduction in the size of the nidus and a reduction in the rate of AV shunting were not effective (86).

Preradiosurgical Embolization

Gobin et al. reported the results in treatment of 125 patients with embolization and radiosurgery. Approximately half of the AVMs had diameters greater than 4 cm and most were Spetzler-Martin grade III or

greater. Embolization cured 11% and made 77% suitable for radiosurgery. Greater than 50% of the AVMs with diameters greater than 6 cm and more than 10% with diameters between 4 and 6 cm did not have sufficient nidal size reduction for subsequent radiosurgery. Overall cure rates were 76% to 78% for AVMs less than 4 cm in diameter, 59% for those 4 to 6 cm, and 7% for those over 6 cm. Therefore, adjunctive embolization was most effective for AVMs of 4 to 6 cm in diameter. There was no convincing advantage for combined embolization and radiosurgery compared to radiosurgery alone for AVMs smaller than 4 cm. Embolization and radiosurgery did not result in a significant cure rate for lesions larger than 6 cm. Preradiosurgical embolization did not provide protection from hemorrhage during the latent period until radiosurgical obliteration. There was approximately a 3% annual rate of hemorrhage during the one to three year follow-up period, similar to the natural history brain AVM hemorrhage rate.

The absence of residual AVM nidus or AV shunting after radiosurgery does not equate with definitive evidence of permanent obliteration of the AVM. Although a negative angiogram had been considered the practical endpoint defining successful treatment, a recent retrospective review of 236 radiosurgery treated AVMs followed for a median of 6.4 years after angiographic evidence of obliteration found four cases of subsequent hemorrhage in the previous AVM site. The two cases that were resected had small regions containing tiny patent AVM vessels. In each case, there was enhancement in the treated site on postgadolinium MRI scans despite normal posttreatment angiograms. The annual risk of hemorrhage was 0.3% (137). Embolization can also be used to treat an AVM persisting after radiosurgery. Marks et al. reported six patients with brain AVMs remaining 24 to 55 months (mean 34 months) after radiosurgery. Embolization resulted in one cure, facilitated surgical resection in three,

and caused sufficient volume reduction in two patients in whom repeat radiosurgery could be performed. There were no complications (96).

Curative Embolization

Published embolization cure rates vary considerably because of selection bias, differing therapeutic goals and techniques. Small AVMs with few feeders have the highest probability of endovascular cure. Case series performed without specific selection of those AVMs that are most likely to be cured by embolization alone, have reported an overall durable embolization cure in 5% to 40% of patients (90,138–140). Valavanis and Yasargil had a 74% rate of curative embolization in a subgroup of patients with favorable angiographic features such as one or few dominant +feeders, no perinidal angiogenesis, and a fistulous nidus versus a 40% rate of curative embolization for their entire series of 387 patients (139). In our series , a total 15 patients out of 78 could have complete nidal obliteration therby acting as curative embolization.

Palliative Embolization

In general, palliative embolization does not appear to improve on conservative medical management and may even worsen the subsequent clinical course. Kwon et al. obtained long-term follow-up in a group of 27 patients with inoperable brain AVMs. Out of these patients, 16 were treated medically and 11 were partially embolized. There was no significant difference between the two groups with respect to clinical improvement, lack of change, and deterioration. In addition, 46% of the partially embolized group experienced hemorrhage in the follow-up period versus 25% in the nonembolized group ($p = 0.27$) (100).

Miyamoto et al. obtained 49-month (mean) follow-up of 46 patients with unresectable AVMs treated with various palliative techniques (partial

embolization, radiosurgery, subtotal resection, and feeder ligation). There was a 14.6% annual rate of hemorrhage, 23% incidence of new major neurological deficits, and a 9% mortality rate (141).

Nonetheless, palliative embolization can be beneficial in selected circumstances. Ischemic neurological deficits caused by vascular steal and venous hypertension in a high-flow, inoperable AVM were improved following partial embolization (102). In another patient, hemifacial spasm caused by a dilated lateral mesencephalic vein draining an inoperable temporo-occipital AVM was cured by selective trans- venous embolization (101). Embolization of dural supply can alleviate intractable headaches. In patients with repeated hemorrhages, targeted embolization of angioarchitectural risk factors such as proximal and nidal aneurysms can limit additional bleeds (103).

Complications

The reported incidence of overall complications from brain AVM embolization varies from 3% to 25% (88,108,134,138,142). The rates of permanent morbidity and mortality in large series range from 3.8% to 14% and 1.0% to 3.7%, respectively (143). Most are caused by hemorrhagic and ischemic events (103). Since complications are related to a number of technical and hemodynamic factors, this wide range in reported rates probably reflects at least, in part, differences in case selection, embolization techniques, and management strategies. In 1995, Frizel and Fisher reported a review of 32 case series of brain AVM embolizations in a total of 1246 patients over 35 years from 1969 to 1993. Overall temporary and permanent morbidity were 10% and 8%, respectively. Overall mortality was 1%. There was no significant difference in permanent morbidity and mortality in the patients treated before and after 1990 (140). In 2002, Hartmann et al. prospectively evaluated 233 patients undergoing

545 embolizations. Thirty- three patients (14%) had treatment-related neurological deficits; however, they were persistent and disabling in only five patients (2%). There were two deaths (1%). Factors statistically associated with new deficits were increasing patient age, absence of a pretreatment deficit, and the number of embolization sessions (144). In 2004, Taylor et al. reviewed 339 AVM embolizations performed in 201 patients over an 11-year period. There was a 7.7% rate of major complications per procedure. Nine percent of the patients had a permanent neurological deficit and 2% died from the embolizations (145).

In 2006, Haw et al. reported the results of 513 attempted embolizations in 306 patients performed between 1984 and 2002. There were eight (2.6%) deaths, six caused by hemorrhage and two caused by ischemic strokes. The rate of death and permanent disabling morbidity was 3.9%. Three factors were statistically associated with complications: an eloquent AVM location, a AV fistula, and venous deposition of the embolic agent (cyanoacrylates). Passage of the embolic agent into the draining veins caused 8 of the 12 (67%) deaths or disabling deficits. There was a reduction in complications producing death or permanent disability in the second half of the study. The authors suggest this was due to advances in equipment and techniques, as well as greater expertise and clinical judgment gained through experience (143).

Types of complications

1. Periprocedural hemorrhage There are a number of causes of periprocedural hemorrhage from brain AVM embolizations. Technical factors include catheter or guidewire-induced arterial perforations, dissections, rupture of aneurysms, vascular injuries during catheter retrieval, and accidental embolizations of venous outflow (109,143). Physiological factors include venous outflow thrombosis, hemodynamic

changes in the setting of impaired cerebrovascular reactivity, and hemodynamic stresses on angioarchitectural weak sites such as feeder, nidal, and venous aneurysms. Embolization can markedly reduce flow through a fistulous nidus causing stagnation in the draining veins. This can result in venous outflow thrombosis, nidal congestion, and a delayed hemorrhage or a venous ischemic infarct (128,143,146). Normal perfusion pressure breakthrough is another important physiological cause of hemorrhage following AVM treatment. The ‘‘sump effect’’ of a large shunt causes low pressure in the arterial feeders and nearby parenchymal branches. The high flow through the nidus elevates venous pressures. The result is a chronically low cerebral perfusion pressure that can impair cerebrovascular autoregulation. If the shunt is suddenly therapeutically disrupted, there is an immediate increase in arterial pressure and a decrease in venous pressure, with a resulting dramatic increase in the cerebral perfusion pressure. If cerebrovascular autoregulation is impaired, resulting parenchymal hyperperfusion can cause cerebral edema or hemorrhage. Spetzler et al. called this normal perfusion pressure breakthrough and found it was associated with large, high-flow AVMs, poor angiographic filling of normal cerebral arteries, extensive collateral flow (steal) , external carotid supply, and progressive or fluctuating neurological deficits (103,127). The risk of normal perfusion pressure breakthrough–induced hemorrhage can be minimized by stepwise reduction in the degree of shunting in large, high-flow AVMs through multiple embolizations staged every three to four weeks, facilitating the gradual recovery of normal vascular reactivity (103). Prompt surgical evacuation of an embolization induced cerebral hematoma results in a good outcome in most cases. Jafar and Rezai reported the emergent surgical evacuation of acute intracerebral hematomas from brain AVMs in 10 patients experiencing acute neurological deterioration, including eight cases occurring after

embolization. They employed immediate intubation, hyperventilation, osmotic diuresis, barbiturate anesthesia, and surgery. The hematoma was evacuated and the AVM was totally resected if possible (8 out of 10). Postoperative cerebral perfusion pressure was maintained above 55-mm Hg with mannitol and barbiturates. Nine of the 10 patients had good to excellent outcomes (147).

2. Ischemic stroke Technical causes of acute stroke during embolization include the showering of NBCA droplets from the catheter tip as it is removed, catheter or guidewire-related arterial dissections and thromboemboli, the embolization of en passage or pseudoterminal supply to normal brain parenchyma distal to the nidal supply, and the inadvertent reflux of embolic material into normal branches proximal to the catheter tip. Ischemic stroke can result from retro-grade thrombosis in stagnant feeding arteries propa-gating into branches to normal brain (148). Delayed venous thrombosis can cause a venous infarct (146). Careful attention to the angioarchitecture on superselective angiography and to an optimal embolization technique will minimize these events (143).

Other complications Embolization with cyanoacrylates has caused permanent adhesion of the microcatheter tip to the embolized vessel in a small percentage of cases. This incidence has decreased significantly in recent years with the use of NBCA and now Onyx rather than isobutyl cyanoacrylate, a wedged microcatheter position to prevent proximal reflux, more dilute NBCA/ethiodol mixtures with slower polymerization rates, and more durable microcatheters with hydrophilic coatings. Careful technique also is important. Redundant loops should be removed before embolization, and the microcatheter should be aspirated and pulled briskly during removal (109).

3. Retained catheters : usually can be transected and buried in the femoral arteriotomy without adverse sequelae; however, brain and lower extremity ischemic complications have been reported (143,149).

4. Pulmonary emboli (PE) have been reported with both particulate and liquid embolic agents. Most are asymptomatic, although respiratory distress and death have occurred. The risk of PE using NBCA is increased with high-flow fistulas, with the use of ethiodol or glacial acetic acid to slowthe polymerization time and by not using flow-arrest techniques. PE were found in 12 (35%) of a series of 47 pediatric patients after brain AVM embolization. The large majority (45) were asymptomatic and found incidentally on chest X rays. The most common agent was cyanoacrylate (10 out of 12), causing respiratory distress in two (150). A retro-spective review of 182 patients embolized with cyanoa-crylates found three cases of symptomatic PE, associatedwith the embolization high-flow AVMs with-out the use of flow-arrest techniques (151).

Multistage angiographic and embolization procedures result in significant radiation doses. Temporary alopecia has been reported, which typically occurs after a short-term radiation dose of 3 to 6 Gy (152).

In our series, 6 (7.6%) patients had hemorrhagic complications .Parenhcymal hematoma was seen in 4 patients. One of this patient died in the post procedure period.One patient was successfully operated and had residual hemiparesis which showed partial improvement with physiotherapy.Two patients showed spontaneous regression of hematoma on conservative management. Two patients had SAH which resolved on conservative management without any clinical sequel.

Among 4 (5%) ischemic complications, one patient had MCA branch occlusion intraprocedure which was thrombolysed without significant clinical deficit. One patient had lateral medullary infarct and another had ACA branch occlusion – both these had residual deficits on

follow up. Two other patients had minor stroke like events from which they fully recovered.

Among other complications, contrast extravasation was seen in 4 (5%) patients during procedure. In 3 patients, this was sealed using glue while in1 patient it spontaneously sealed off. Catheter gluing was seen in 7 patients in whom it had to be cut at groin. In two patients Ultraflow microcatheter ruptured – it was fully removed in one while broken fragment pushed to ECA branch in other. One patient had guidewire induced small CCF which sealed off spontaneously after some time.

Five (6.4%) patients had seizures in the initial post procedure period which were managed conservatively.

Considering residual deficit in 3 patients, overall morbidity rate was 3.8% and mortality rate was 1.2 %

Materials and Methods

This was a retrospective study carried out in the department of IS & IR, at SCTIMST, Trivandrum. For the purpose of this study, patients who had undergone endovascular management for brain AVMs in the department of IS & IR, SCTIMST, dating from 1st Jan 2005 to 31th Oct 2011 were included. There were a total of 86 cases in the initial list.

The clinical data of the patients was obtained by reviewing their case sheets obtained from the Medical Records Department & the imaging data was obtained from the DSA lab archive. From these, the data regarding clinical presentation, imaging, angiographic characteristics, details of the embolization procedure, post procedural status and the follow up was collected.

All patients underwent a baseline neurological evaluation prior to the procedure. All the patients had a baseline imaging done – either a CT or MRI of the brain. Subsequently, the patients underwent a complete four vessel diagnostic cerebral angiogram. All the studies were performed on Advantx digital substraction angiography unit (GE Milwaukee, USA) or Innova biplane flat panel digital substraction angiography unit (GE Milwaukee, USA). A wide variety of catheters and embolic material was used for the procedures as was best suited for the individual patient depending on the angioarchitecture.

Diagnostic angiographies were done under local anesthesia when they were performed separate from interventional procedure or performed as a check angiography for follow up. The interventional procedure was done under general anesthesia. Premedication (Inj. Pethidine/ Tramodol 25-50mg i.m & Inj. Phenergan12.5- 25mg i.m)

was given before the local procedures. Post procedure these patients were managed in the wards when angiography was performed under local anesthesia. For procedures carried out under general anesthesia, the patient was monitored in the neurological intensive care unit.

After discharge, the patients were followed up with clinical evaluation for improvement in their symptoms. Follow up imaging or angiograms were evaluated when available.

A complete evaluation of the patient including demographic profiles (age, sex), clinical presentation, imaging features, treatment method and outcome including complications and follow up was carried out as per the proforma attached.

Technique of embolisation:

All procedures were performed via the transfemoral route using the Seldinger technique. The guiding catheters used during the procedure were continuously flushed with heparinized saline (2000 units /L) with systemic heparinisation of 3000- 5000 IU as bolus and 1000 IU every hour monitoring the ACT.

The procedures were performed under general anesthesia. A guiding catheter was placed in the main feeding arteries In anterior feeders, guiding catheter was usually placed in vertical portion of distal ICA and then feeders were selectively cannulated with microcather, In posterior feeders, guiding catheter was placed in V2 segment and then feeders were cannulated and embolized using coil or glue.

Superselective catheterizations and embolic injections were performed, using exclusively variable stiffness microcatheters of either Spinnaker or magic Microcatheter in the older cases (where NBCA or alcohol was used for embolization) and Marathon in cases where onyx was used for embolization .

Decisions regarding injection of embolic material were taken following anatomic evaluation of superselective angiograms and pre-embolisation MR and with the conviction that all brain areas are eloquent.

Onyx (EVOH), Cyanoacrylate (NBCA) and absolute alcohol were the embolic material of choice used in these patients. Onyx alone was used in 32 (41%) cases. Cyanoacrylates were used as the sole embolic material in 19 (24%) cases of this series, 7 (9%) patients were embolized with absolute alcohol, 8 (10%) patients had both NBCA and onyx, 7 (9%) patients were embolized with both NBCA and alcohol and in 5 patients a combination of multiple agents was used. In two cases with high flow fistulae were Bernstein liquid coils used prior to cyanoacrylate embolization, because of angioarchitectural reasons. The techniques of catheterization and embolisation used throughout this series are described in detail later. The catheters and wires used for the purpose are shown in table 1.

Table1 : MATERIAL USED FOR ANGIOGRAM AND EMBOLIZATION

1.	Sheath – Radiofocus, Cordis	4,5, 6, 7 French size
2.	Diagnostic catheters – Vertebral glide (Terumo), Right coronary (Cordis), Mani cerebral (Cordis), Simmons (Cordis), Multipurpose (Cordis)	5, 4 French size
3.	Guide wire – Terumo exchange length, Terumo standard,	150 cm – Standard 260 cms - Exchange
4.	Guiding catheters – Vistabrite, Launcher (Cordis), Neuron	6, 7 French size
5.	Microcatheters – Spinnaker, Magic, Mararthon	1.5 to 1.8 French
6.	Microguidewires – Transcend, Mirage.	.008, .010 of varying length (190-205cm)
7.	Embolic materials –Glue (N-Butyl Cyanacrylate - NBCA), Absolute alcohol, Onyx 18	Glue 17%-80%

Immediate post embolisation brain CT was done in those cases with suspicion of complication. Patients with AVMs in which a complete obliteration was achieved, had follow up MR/CT or angiography following the last embolization session at variable intervals ranging between 1 month to 3 years 6 months. Follow up data from all patients were obtained from hospital case record , during their OPD visit and also telephonic conversation with patients or their immediate relatives.

Results

Demographic profile

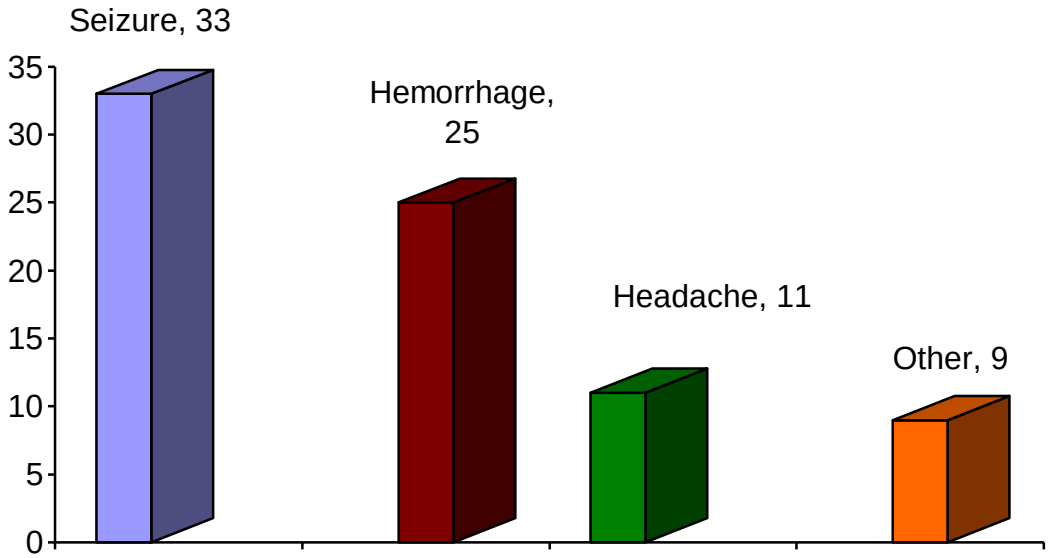
There were a total of 86 cases initially. However, only patients with sufficient clinico radiologic data were included in the study. The final list thus included 78 patients. The age of the patients ranged between 10-56 years (mean 30.7 years) and male to female ratio was 60: 18. The distribution in various decades of life is as follows:-

Age group(yrs)	**Number of patients**
0-9	Nil
10- 19	19
20- 29	20
30- 39	19
40-49	12
50-60	8

Clinical Features

Commonest presenting feature was seizures(33 patients, 44%) next was hemorrhage (25 patients, 32%), then head ache (11patients, 14%) and weakness and non specific complaints (9 patients, 11%).

Fig 1: Distribution of clinical presentation



Angioarchitecture

Location

AVMs *located* in one lobe showed preponderance in frontal (20), then parietal (11), followed by temporal and occipital. AVMs involving 2 lobes commonly involves parieto-occipital (13) followed by fronto parietal (11) lobes. AVMs involving more than 2 lobes all cases were in the tempero parieto occopital areas.

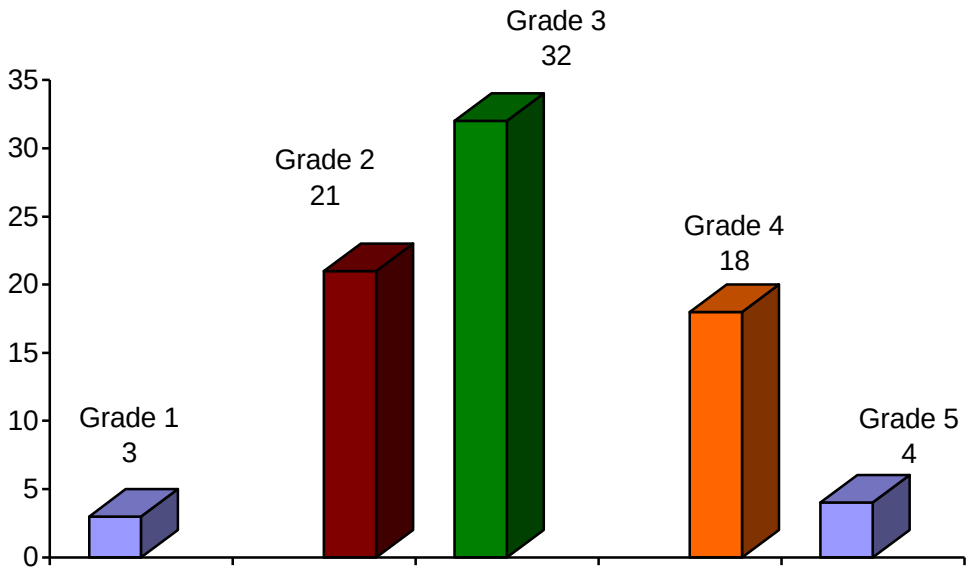
Size

Of the 3 orthogonal measurements usually taken for AVMs, the maximum dimension of AVMs in any direction varied from largest 7 cm to smallest 0.4cm.

Grading

Spetzler Martin grading was applied to these AVMs based on location, size and venous drainage pattern on evaluation of angiographic images. AVMs in grade 1 were 3, those in grade 2 were 21 and remaining (53) were of high grade type (grade 3,4 and 5). 18 patients with AVM showed exclusive deep venous drainage.

Fig 2: Distribution of Spetzler Martin Grade



Other features (aneurysmal changes/ venous ectasia or stenosis)

6 Patients showed intranidal aneurysms whereas 5 patients showed feeding artery aneurysms. 9 patients showed venous pouches/ focal ectasias. Of the 10 patients showing feeding artery or nidal

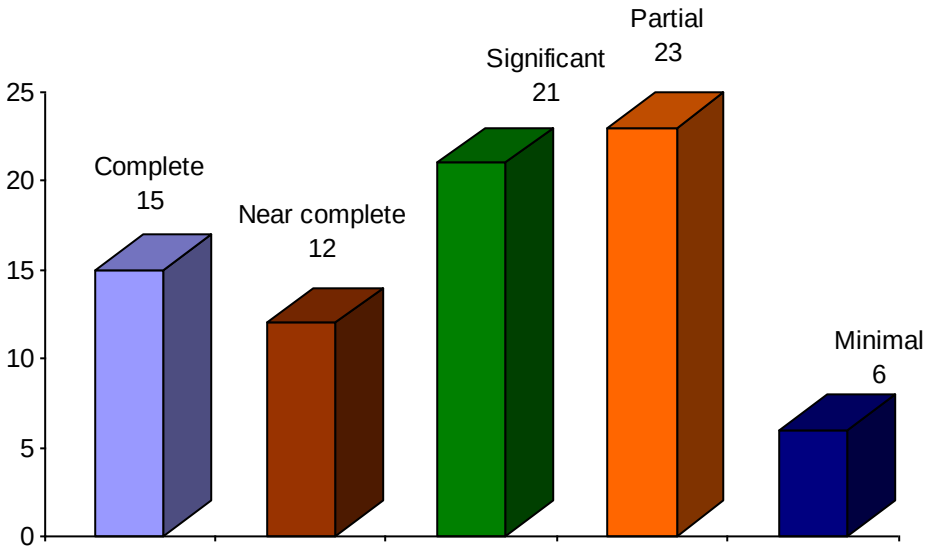
aneurysms, 5 had presented with hemorrhage. In the group of 25 patients who had presented with hemorrhage, 17 had smaller nidus (less than 3 cm maximum dimension). No definite preponderance of deep venous system drainage could be seen in the hemorrhagic group.

Management

A Total of 78 patients were embolized during the period.11 patients had 2 sittings of embolization. 3 patients had 3 sittings of embolization and 3 patients had more than 3 sittings of embolization. Maximum embolization attempts were 6 in one patient. . Onyx alone was used in 32 (41%) cases. Cyanoacrylates were used as the sole embolic material in 19 (24%) cases of this series, 7 (9%) patients were embolized with absolute alcohol, 8 (10%) patients had both NBCA and onyx, 7 (9%) patients were embolized with both NBCA and alcohol and in 5 patients a combination of multiple agents was used. In two cases with high flow fistulae were Bernstein liquid coils used prior to cyanoacrylate embolization, because of angioarchitectural reasons.

For the purpose of description , the extent of embolization has been divided into complete (100%), Near complete (90-100%), Significant (70-90%), Partial (20-60%) and Minimal (less than 20%). 15 cases showed complete nidal obliteration, 12 cases showed near complete obliteration, 21 cases showed significant obliteration whereas 23 patients showed only partial obliteration. In 6 cases no or minimal obliteration could be achieved, either because of angioarchitectural reasons or because the patients refused further embolization sessions.

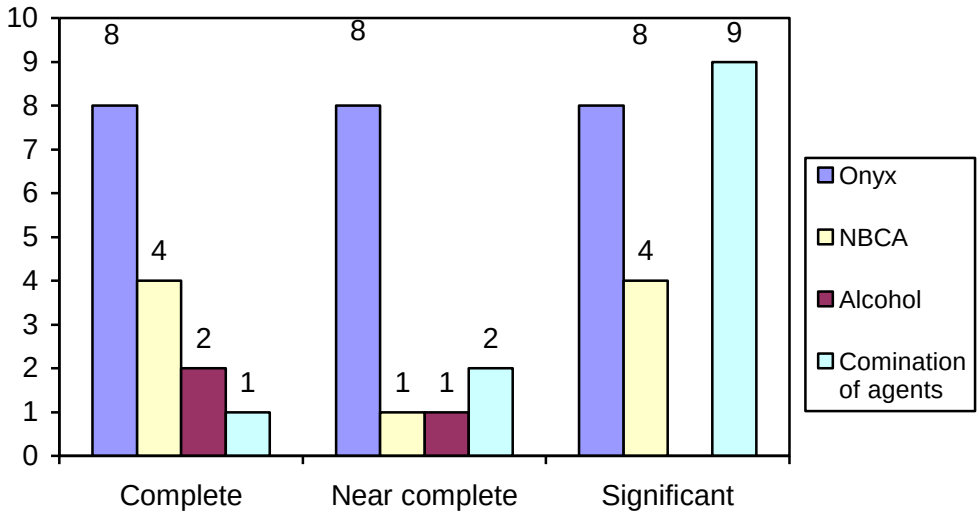
Fig 3a: Extent of AVM nidus obliteration after embolization



The angioarchitecture features favoring *complete embolization* were small size (7 /15) and feeders from ACA only (8/15), especially when only one or two prominent feeders were there.

Of the 27 patients showing complete or near complete embolization, Onyx was used as embolizing agent in 18 cases, NBCA was used in 5 cases, alcohol was used in 2 cases and combination of agents was used in 2 cases. In 21 patients showing significant obliteration, onyx was used in 8 cases, NBCA was used in 4 cases and a combination of agents (usually NBCA and alcohol) was used in remaining cases.

Fig 3b: Extent of AVM nidus obliteration and Embolizing agent used



In the 51 patients who had only partial or minimal embolization of nidus, Stereotactic Radiotherapy (SRT) was carried out in 21 patients and these are on follow up. Surgical excision was carried out in 3 patients where no residual nidus was demonstrated on radiologic follow up. In 8 patients with mainly large and angioarchitecturally complex AVMs or with diffuse type of nidus only palliative embolization either targeted on weak angioarchitectural elements or to palliate chronic severe headaches was performed. One patient died in the post procedure period and 9 patients were lost to follow up. Other patients are on clinico – radiologic follow up or are awaiting next session embolization.

Clinical follow up

Variable clinical response was seen in patients post procedure. A significant number (21/33) of the patients presenting with seizure had significant decrease in the symptoms resulted in the reduction of seizure frequency and anti epileptic drugs. 5 patients showed

increase of symptoms whereas remaining showed no significant change in frequency of seizures.

In the 25 patients who had presented with hemorrhage, 2 patients bled again in the immediate post procedure period. One of these patient eventually died while timely surgical evacuation of frontal hematoma in the second could improve his hemiparesis partially with conservative management and physiotherapy. Four of these patients presented with re bleed for which urgent re – embolization was done

Six out of 11 patients who had presented with headaches showed significant improvement in the symptoms while 2 patients had mild improvement in symptoms.

Complications

For the purpose of description, complications may be divided into major or minor. Major complications included hemorrhagic or ischemic events. Minor complications included small contrast extravasation, catheter gluing or rupture, seizures, infections and small spontaneously resolved CCF.

Among major complications, 6 (7.6%) patients had hemorrhagic complications .Parenhcymal hematoma was seen in 4 patients. One of this patient died in the post procedure period.One patient was successfully operated and had residual hemiparesis which showed partial improvement with physiotherapy.Two patients showed spontaneous regression of hematoma on conservative management.Two patients had SAH which resolved on conservative management without any clinical sequel.

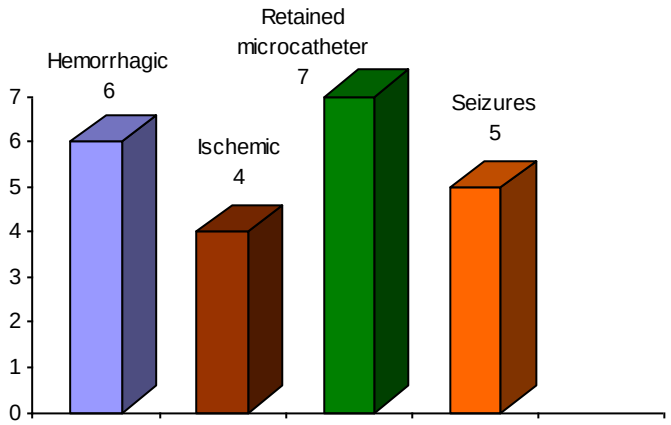
Among 4 (5%) ischemic complications, one patient had MCA branch occlusion intraprocedure which was thrombolysed with Urokinase without significant clinical deficit. One patient had lateral medullary infarct and another had ACA branch occlusion – both these had residual deficits on follow up. Two other patients had minor stroke like events from which they fully recovered.

Among other complications, contrast extravasation was seen in 4 (5%) patients during procedure. In 3 patients, this was sealed using glue while in1 patient it spontaneously sealed off. Catheter gluing was seen in 7 patients in whom it had to be cut at groin. In two patients Ultraflow microcatheter ruptured – it was fully removed in one while broken fragment pushed to ECA branch in other.

One patient had guidewire induced small CCF which sealed off spontaneously after some time. Five (6.4%) patients had seizures in the initial post procedure period which were managed conservatively.

Considering residual deficit in 3 patients, overall morbidity rate was 3.8% and mortality rate was 1.2 %

Fig 4: Important Complications



Discussion

The study was carried out with an aim to assess epidemiologic, clinical and management aspects in all the AVM cases who were treated at a tertiary care referral institute, with a focus to generate data in Indian context as most of the extensively published data has been from the western literature.

The study included 78 patients treated in this institute between Jan 2005 and Oct 2011. Patients showed spreadout distribution among second to seventh decades with mild preponderance in third to fifth decade. In a recently published systematic review and meta- analysis by Van Beijunum et al (JAMA , 2008) also, the median age among 13698 patients was 34 years (range 10-54 years) (155*)*. In another large series of 1289 patients published by Las Jaunias et al (Stroke, 2000), the median age was 31.2 years (range 0-60 and above) (156) . Hence our findings are in concordance with available data ; our mean age being 30.7 years (range 10 –seventh decade).

However, important to note is that no patients were there in first decade. This is a paradoxical finding with reference to presumed congenital etiology of AVMs. This is in concordance with the aforesaid meta- analysis and at a variance with the findings of Las Jaunias group Possible reasons for this may be the presence of occult AVM which manifest only later once the hemodynamic stress adds on to the vulnerable vasculature of AVMs. Also lack of adequate infrastructure facilities and awareness among general practitioners in remote locations may delay the initial diagnosis.

The male to female ratio (60:18 – 3.4:1) in our study showed a strong male preponderance . In both the above quoted large studies, the male to female ratio was 1.2:1.0, thus not showing any gender preponderance. This may be explained partially by lack of awareness and

adequate facilities to women, especially in remote locations. However, an ethnic gender predisposition for male patients can not be ruled out and needs to be evaluated further by more studies.

The clinical presentation of the AVMs can be classified broadly into hemorrhagic and non hemorrhagic which determines the urgency and necessity to treat them to a significant extent. Among hemorrhagic manifestations, the most often reported occurrence is that of parenchymal bleed . The bleed may show intra ventricular extension at times or may also extend into subarachnoid space. At times, the AVMs may also present with SAH alone without parenchymal hematoma (14, 19, 20, 21, 22). In a prospective population-based study published in 1996, 65% of patients newly diagnosed with a brain AVM presented with intracranial hemorrhage (22). Intraparenchymal hemorrhage occurred in 41% of these cases, subarachnoid hemorrhage in 24%, intraventricular hemorrhage in 12%, and a combination of these types in 23% of cases. The more recent prospective population-based study of brain AVMs in the New York Islands reported that 38% of patients with newly found AVMs presented with intracranial hemorrhage (19). The Lasujaunias group (ii) reported 51% of their patients presenting with hemorrhage. In our study, 25 of 78 patients (32%) presented with hemorrhagic manifestations. This is slightly on lower side as compared to the literature. Part of it may be failure to identify the cause at peripheral medical centres. However, it may also be related to other genetic and other differences in western and Indian population groups which needs to be studied further.

The non hemorrhagic manifestations seen in our study were seizures (33 patients, 44%), head ache (11patients, 14%), weakness/ sensory stroke (4 patients, 5%) and non specific complaints such as giddiness, facial pain, head discomfort or incidentally detected (5 patients, 6%). In the

literature, the second most common form of clinical presentation is epilepsy. In one retrospective population-based study, 19% of newly discovered AVMs presented with seizures (22). In two retrospective hospital-based studies, 18% and 27% of AVMs presented with seizures, respectively (30,31).Other less common brain AVM presentations include headache (1% and 11% in two hospital-based series) (30,31), focal neurological deficit (7% and 5% in two hospital-based series) (30,31), and as an incidental finding in an asymptomatic individual (15% in one population-based study, 0.5% and 3% in two hospital based series) (22,30,31).In the series published by Las Jaunias et al *(ii)* seizures were seen in 40%, neurodeficits in 14% and headache in 7% patients.

The higher occurrence of epilepsy in our series may be partially attributed to well established national level epilepsy centre in our institute. Other manifestations are more or less in concordance with the literature in being not so common presentation of AVM. It is important to note that the prevalence rates for these less common manifestations are as such significantly variable in literature as mentioned above.

As far as angioarchitecture features are concerned, most of the AVMs in our series preponderance of frontal location (24%), compact nidus (80%), intermediate Spetzler Martin Grade (Grade 2 and 3 most common as described in results) and variable size. Feeding artery aneurysms were seen in 5 patients, 6 patients showed nidal aneurysms. 8 patients showed exclusive venous drainage, 26 patients showed mixed (superficial as well ass deep) and remaining showed superficial venous drainage. 9 patients showed venous ectasia or aneurysmal dilatations. Of the 11 patients showing feeding artery or nidal aneurysms, 5 (45%) had presented with hemorrhage. In the group of 25 patients who had presented with hemorrhage, 17 had smaller nidus (less than 3 cm maximum dimension).

No definite preponderance of deep venous system drainage could be seen in the hemorrhagic group. The association of smaller nidal size, feeding artery and nidal anueyrsm has been well described in literature and was seen in our series also. However, the relationship between deep venous drainage and hemorrhage was not seen in our series. This raises the probability as to other venous angioarchitecture factors such as single draining vein, venous stenosis or aneurysm play more important role in hemorrhagic manifestations.

The endovascular management of AVMs has shown significant progression in last few decades. Initially, PVA particles were used for embolization (89) with unsatisfactory results and higher recurrence rates. The next major development was seen with advent of liquid embolic agent NBCA which was approved by the FDA in 2000. However, the embolization of AVM became technically more feasible with advent of Onyx which has become the most popular embolic agent in last few years. In a prospective randomized control trial, 117 patients were embolized with NBCA (63) or Onyx (54) between May 2001 and April 2003. More than 50% nidal obliteration was seen in 85% of NBCA and 96% of Onyx group. Various other hospital series have also shown higher nidal obliteration rates with Onyx.

In our series, 15 cases showed complete nidal obliteration, 12 cases showed near complete obliteration, 21 cases showed significant obliteration whereas 23 patients showed only partial obliteration. In 6 cases no or minimal obliteration could be achieved. The nidus which could be completely or near completely obliterated were usually small, had few feeders and mostly with the use of Onyx as embolic agent. Of the 27 (34%) patients showing complete or near complete embolization, Onyx was used as embolizing agent in 18 (55%) cases, NBCA was used in 5 (6.5%) cases,

alcohol was used in 2 cases and combination of agents was used in 2 cases. Thus again, superiority of Onyx over other agents in AVM embolization is clearly demonstrated.

The complications associated with AVM embolization have produced variable morbidity and mortality with better results in the recent years. A summary of morbidity and mortality rates on literature review is shown in table below

S No	Authors & Year	No of patients	Mortality (%)	Morbidity (%)
1.	Frizzel & Fisher 1995	1246	1.0	8.0
2.	Yasargil et al 1998	387	3.7	5.6
3.	Hartmann et al, 2002	233	1.0	14.0
4.	NBCA trial, 2002	54	1.9	13.0
5.	Present series	78	1.2	3.8

In our series, Among major complications, 6 (7.6%) patients had hemorrhagic complications .Parenhcymal hematoma was seen in 4 patients. One of this patient died while other could be salvaged by urgent surgery in the post procedure period. Among 4 (5%) ischemic complications, one patient had MCA branch occlusion ,one patient had lateral medullary infarct and another had ACA branch occlusion – both

these had residual deficits on follow up. Two other patients had minor stroke like events from which they fully recovered.

Among other complications, contrast extravasation was seen in 4 (5%) patients during procedure. In 3 patients, this was sealed using glue while in1 patient it spontaneously sealed off. Catheter gluing was seen in 7 patients in whom it had to be cut at groin. One patient had guidewire induced small CCF which sealed off spontaneously after some time. Five (6.4%) patients had seizures in the initial post procedure period which were managed conservatively.

Considering residual deficit in 3 patients, overall morbidity rate was 3.8% and mortality rate was 1.2 % which is less as compared to most of the series quoted in literature above.

To sum up, our series demonstrates preponderance of male patients in third to fifth decades, mostly presenting with seizures or intracranial hemorrhage. Most of the patients presenting with hemorrhage had small nidus with presence of feeding artery or nidal aneurysms increasing the chance of hemorrhage. 34% patients (27/76) could have complete or near complete embolization, mostly in case of small AVMs with few feeders and with the use of Onyx. The complication rates were less than that quoted in literature. These experiences may be further utilized in selecting the patients and targeting at early or delayed and aiming at curative or partial embolizations.

Conclusion

Brain AVMs are very heterogeneous, rare central nervous system vascular malformations associated with significant long-term morbidity and mortality. Embolization has become an increasingly important therapeutic option, usually in combination with surgery or stereotactic radiosurgery. It is, however, associated with risks that must be considered in the context of the overall treatment plan. A multispecialty team comprised of experts in vascular neurosurgery, interventional neuroradiology and radiosurgery optimally manages brain AVMs.

Rapid advances in technology have had a profound impact on brain AVM embolization, and the innovations promise to continue. Dramatic improvements in microcatheter and guidewire technology have led to the superselective catheterization of distal cerebral arteries. This has led to a better understanding of AVM angioarchitecture and has enabled the intranidal embolization of AVMs with liquid embolic agents. Nonetheless, further work is required to improve the safety and efficacy of embolization, and more rigorous data on the natural history of brain AV Ms and treatment outcomes are needed.

This study showed that in carefully selected group, 19% (15/78) of patients with brain AVMs could be cured by embolization alone with a morbidity of 0.5% and a mortality of 0.1%. Further, in another 15 % (12/78) patients, near complete embolization could be achieved. If appropriately selected, embolization alone may prove to be curative in almost 1/3 of patients. The factors which favour complete or near complete embolization

were small size (usually <2cm and especially micro AVMs), one or few feeders from same vascular territory and a location in ACA territory.

Post procedure stereotactic RT or microsurgical assistance may further increase the cure rates. Which modality will be chosen for a particular patient will mainly depend on the locally available expertise and experience, but also on the preference of the patient following its comprehensive information about the chances for cure and the risks associated with each of these therapeutic modalities. Post embolization radiotherapy or surgery has increased the cure rate up to 36% in this case.

Embolization has thus a significant role in the multimodality treatment of brain AVMs, by either enabling or facilitating subsequent microsurgical or radiosurgical treatment. Appropriately targeted embolization in otherwise untreatable AVMs represents a reasonable form of palliative treatment of either ameliorating the clinical condition of the patient or reducing the potential risk of hemorrhage.

This series also helped us in reaching following inferences regarding practical management based on observations and outcomes on analysis of data :-

1. The risk to benefit ratio should be carefully assessed before embolization. Many patients with occasional headache or well controlled seizures with no other high risk angioarchitecture related features, may simply be followed up.

2. Once treatment is decided and endovascular option is to be used, aim of endovascular treatment should be defined prior to the procedure. In carefully selected patients, we may aim for curative embolization whereas

in others, only pre surgical /pre RT embolization, targeted or palliative embolization may be carried out.

3. The next step after endovascular therapy should already be planned so that patient gets holistic treatment with an aim to completely obliterate the nidus.

4 .Atraumatic superselective micro catheterization is a key point in the endovascular treatment of brain AVMs. It requires manual skills, knowledge of anatomy and respect for the vascular wall.

5. Embolization should be performed only after the particular angioarchitecture has been fully appreciated and the particular compartment to the embolized has been precisely localized with angiographic MR correlation.

6. Onyx shows better nidus obliteration rates as compared to NBCA (18 cases vs 5 cases in this series) and should be the embolic agent of choice as far as possible. However, considering the financial implications or in presence of fistulous component, NBCA may still be used in only few selected cases based on experience of the Interventionist.

7. This series shows relatively lower complication rates compared to quoted rates in Literature. Part of it may be because of use of superior microcatheters and guidewires and use of Onyx. Hence, over time and with further refinements in technology, it may evolve as treatment modality of choice as happened in case of Intracranial aneurysms.

Representative Cases

Case No 1

HISTORY:

51 years male patient presented with complaints of sudden onset headache, difficulty in speech and right sided weakness on 9/12/08. He was treated conservatively at a local hospital and his symptoms improved over the next 4-5 days. He was evaluated and found to have a left parietal AVM. At the time of admission at SCTIMST, he was having mild right sided weakness.

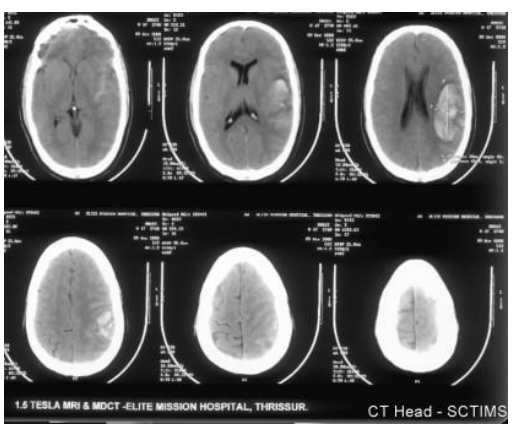
No history of headache, vomiting, loss of consciousness, seizure, visual disturbances, gait disturbances, bladder and bowel disturbances.

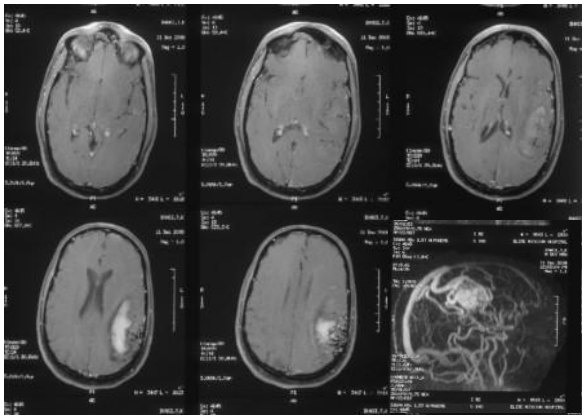
ON EXAMINATION:

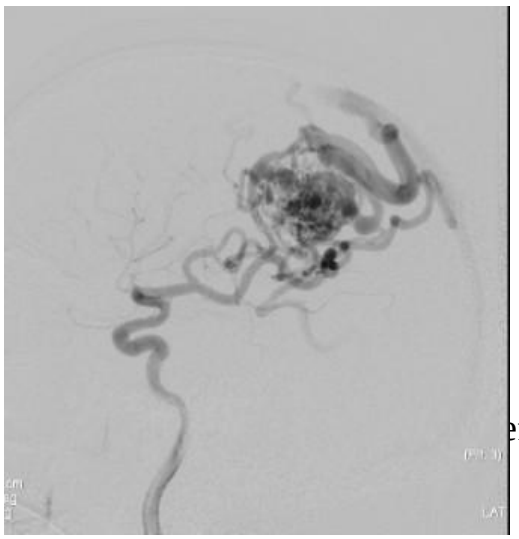
Patient was conscious, alert with stable vital signs. GCS on admission-15/15. Visual fields normal by confrontation. Fundus- no papilledema.

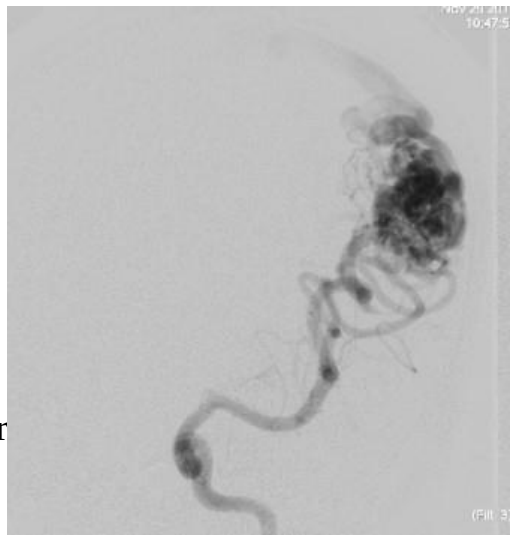
HMF were normal. No cranial nerve deficits were found. Bulk and tone of muscles was normal in all 4 limbs. Power grade 5/5 on left side, 4/5 on right side. DTRS normal. Plantars flexor. No sensory deficits. No cerebellar signs. Other Systemic examination unremarkable.

IMAGING







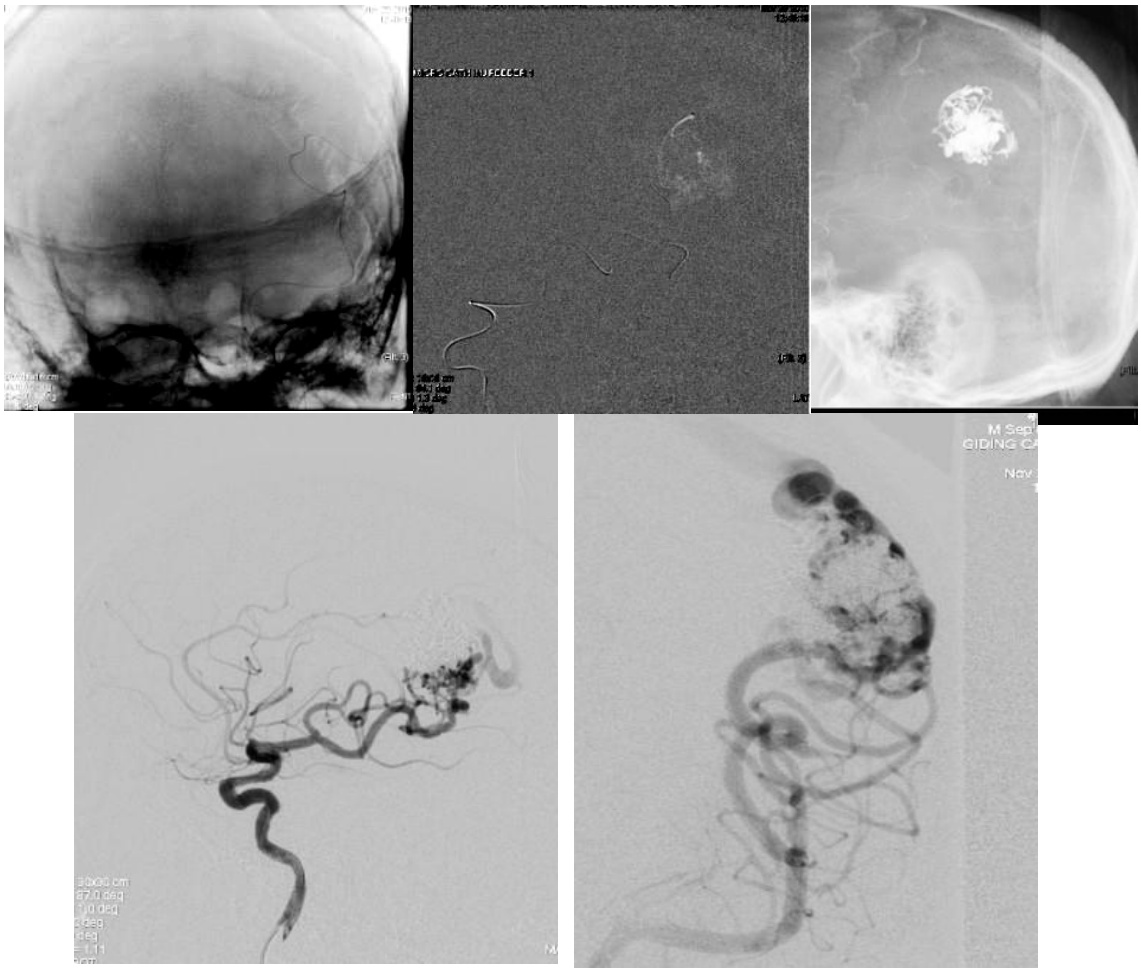


eft fr

MRI Brain (10/12/08) again showed Left frontoparietal bleed with underlying AVM with feeders from MCA and large draining vein into SSS.

DSA was done subsequently (4/3/09) which showed Left parietal AVM 3.4 x 2.0 x 1.7 cms with feeders from left MCA and draining into SSS and left TS. Steal from VB system via PCom. was seen

INTERVENTION



6F guiding catheter was taken with tip in diastal cervical ICA. Marathon flow guided catheter was then canulated into feeding angular branch and 3.4 ml of total Onyx was injected under hypotension & roadmap guidance. Microcatheter tip however, was glued in Onyx mass and could not be retrieved and was cut at sheath end. Check angio showed 70-75% nidus reduction.Small residual nidus was seen in posteroinferior part. Patient was sent for Stereotactic Radiotherapy for management of residual nidus and is stable and on follow up.

Case No 2

HISTORY

29 Year old patient, no known comorbidities, apparently normal 10 months back, came with history of recurrent seuzures for last 10 months.

Semiology - Aura of heaviness of head. Ictus - deviation of hand, uprolling of eye balls, Duration - 3-5 min, Frequency - total of 10 episodes of seizures in last 10 months. Post ictal confusion often present.

Patient also gave history of intermittent holocranial headache.

No history suggestive of any cranial nerve/ motor or sensory deficits

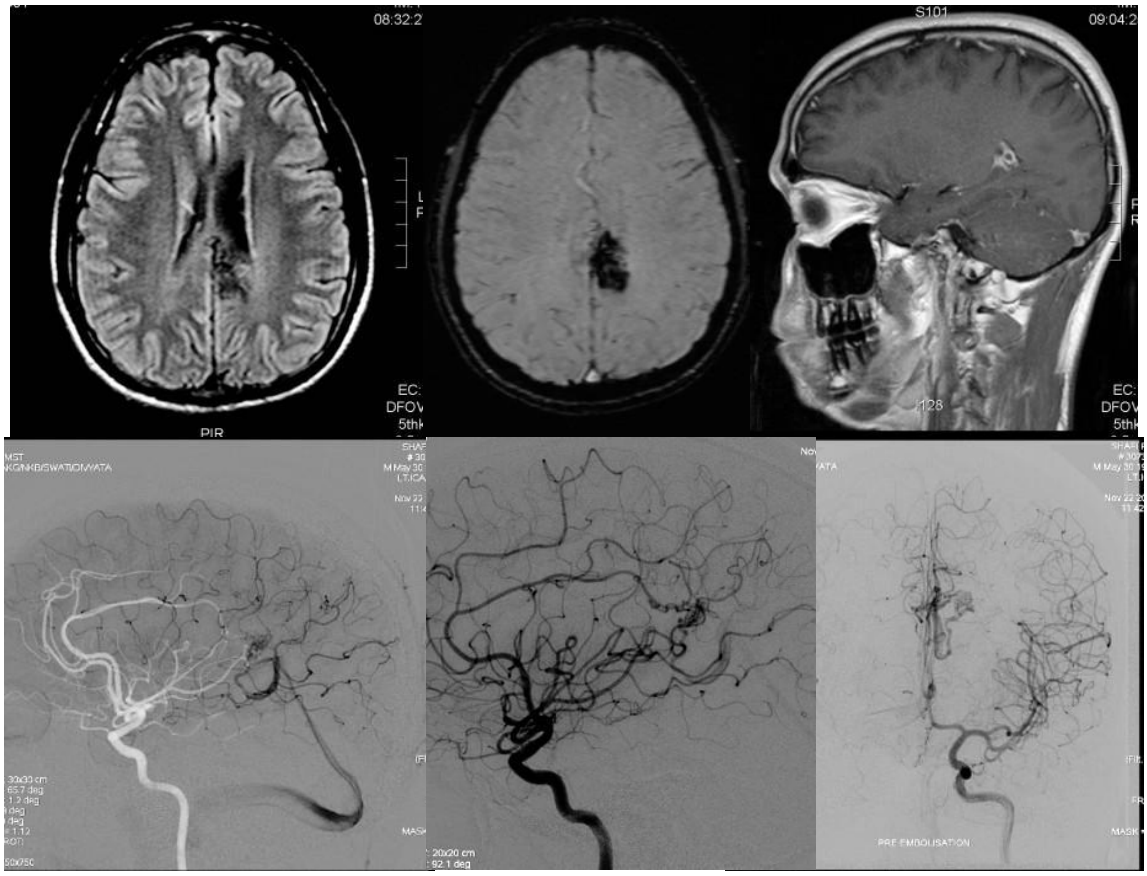
No h/o headache, voimiting, unconsciousness.

ON EXAMINATION

General and systemic examination – no significant positive findings

No positive findings on Neurologic evaluation.

IMAGING

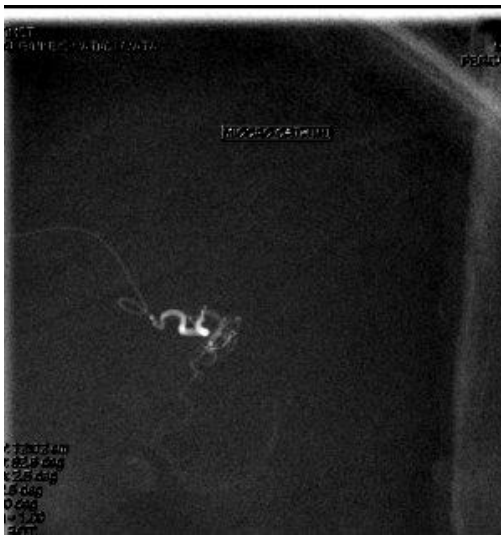


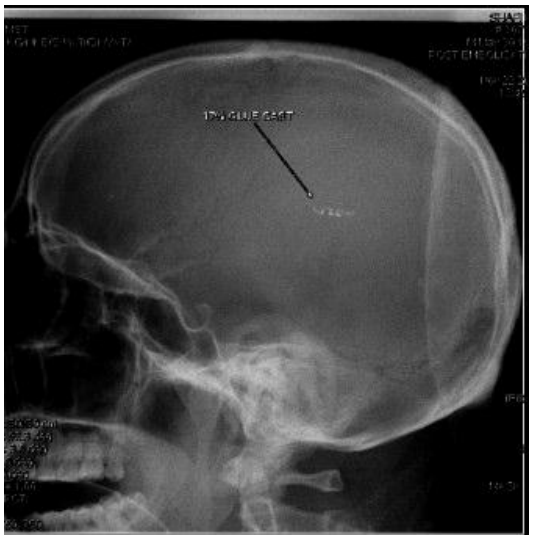
multiple flow void on T1, T2 and FLAIR images noted in left peritrigonal region shows area of blooming on SWI and tangle of enhancing vessel within the lesion raising possibility of small AVM.

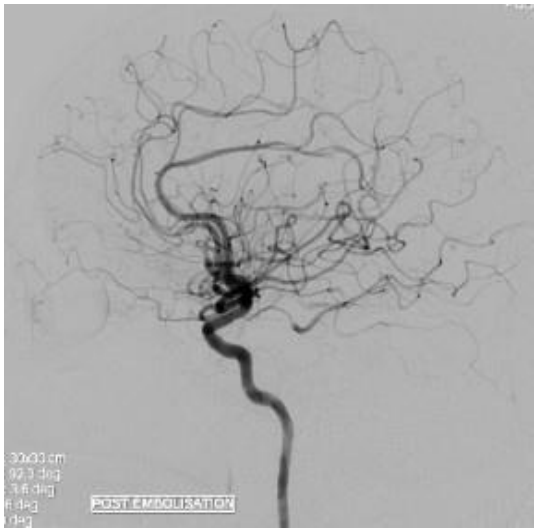
DSA (15/11/2010) showed small compact compact nidus AVM measuring 9.4 x 6 x 9 mm in left medial parietal region fed by splenial branch of pericallosal artery (left ACA). Minimal filling of the nidus was also noted via posterior splenial branch of left PCA.

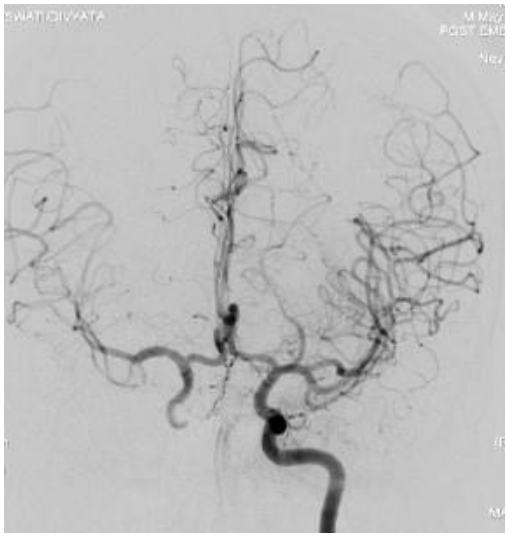
Venous drainage was to the vein of Galen via single draining vein.

INTERVENTION









Under GA, under strict aseptic precautions, right CFA was punctured and 7 Fr sheath was secured. Feeder was selectively catheterized using Marathon catheter. However, it could not be negotiated distally near nidus. Diluted glue 17% was injected. Glue percolated well in the nidus. Few drops crossed to venous side. Check angio showed complete obliteration of the AVM.

Patient tolerated the procedure well. No complications were noted. Follow up DSA after 6 months showed no residual nidus.

Case No 3

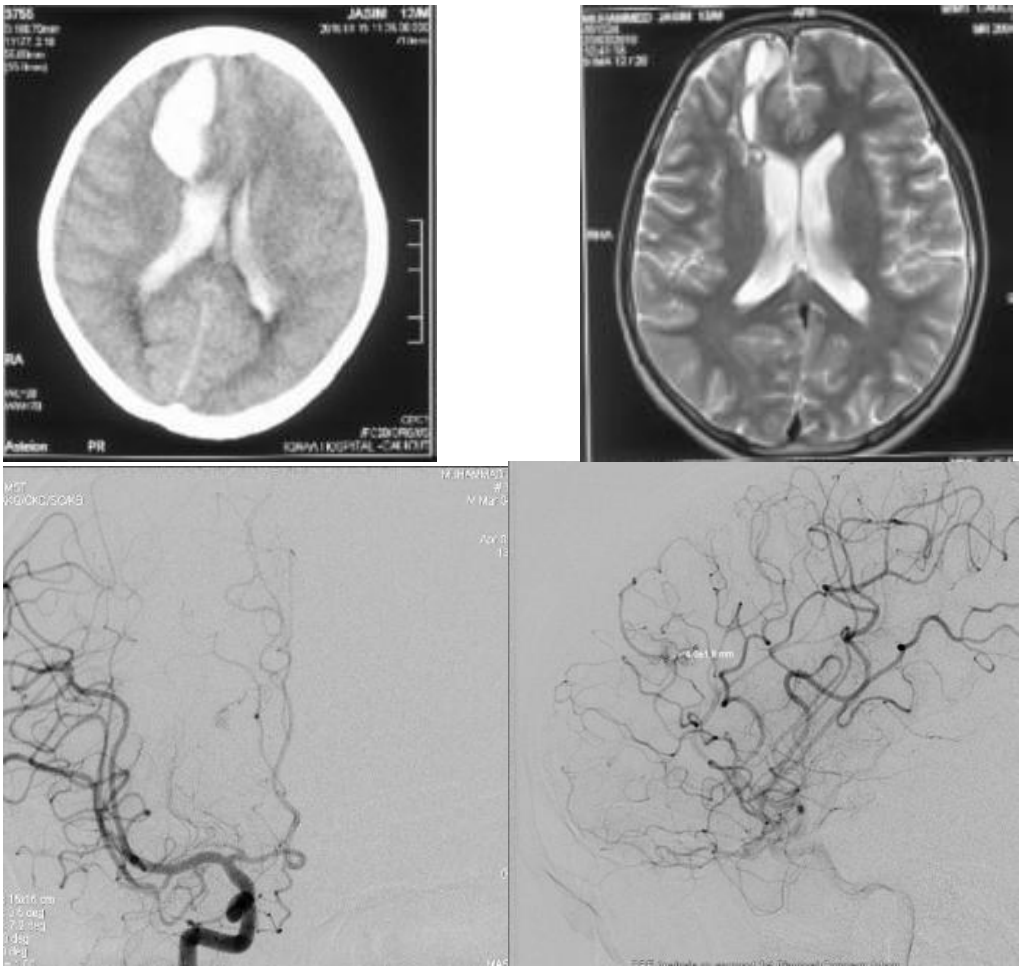
HISTORY: 13 years old boy presented with complaints of severe holocranial headache associated with vomiting on 15/1/10 followed by 1 right sided seizure followed by loss of consciousness. He improved gradually over 2 wks.

No history suggestive of any cranianl nerve, motor or sensory deficits.

ON EXAMINATION: Patient conscious, alert with stable vital signs. GCS on admission-15/15.

HMF was normal. Pupils bilaterally equal and reactive. Extra-ocular movements full. Visual fields normal by confrontation. Fundus- no papilledema. No other cranial nerve deficits. Bulk and tone of muscles normal in all 4 limbs. Power grade 5/5 in all 4 limbs. DTRS normal. Plantars flexor. No sensory deficits. No cerebellar signs. Systemic examination was unremarkable.

IMAGING

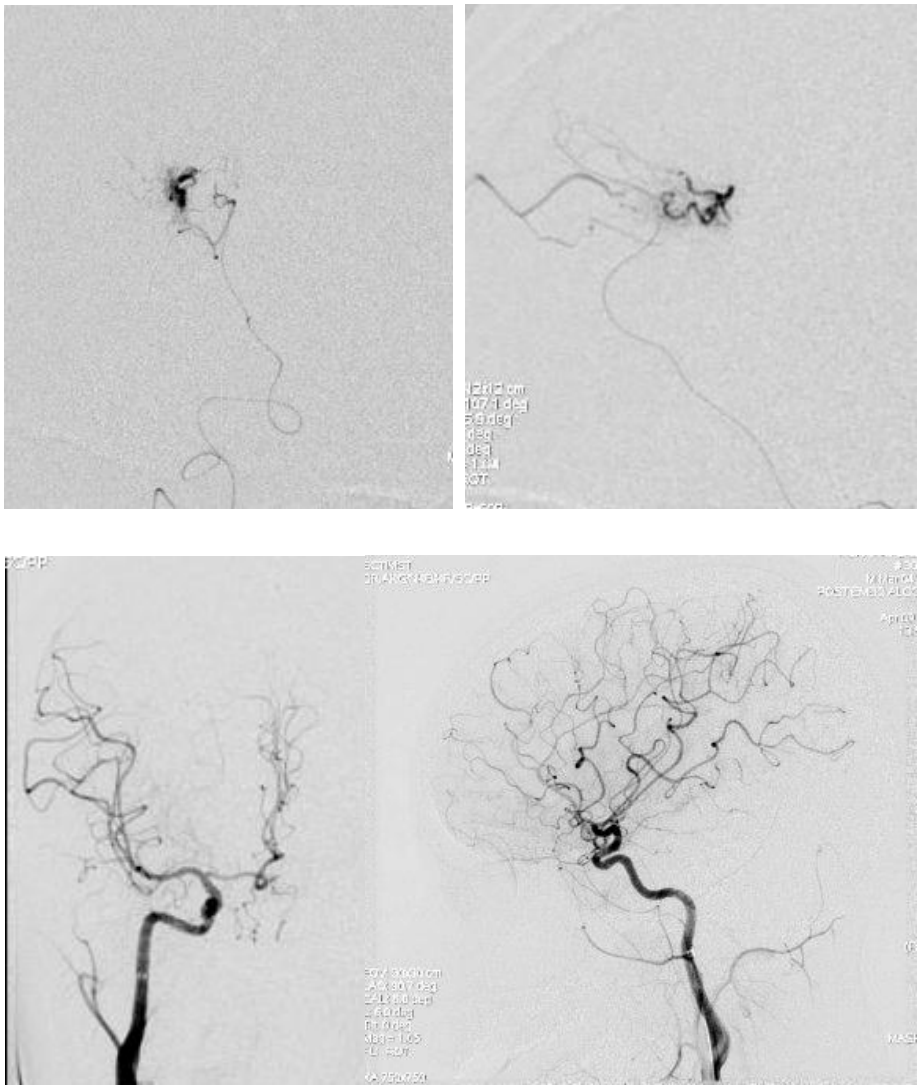


CT (15/01/10) showed large right frontal hematoma with intraventricular extension.

MRI Brain (25/3/10): showed Resolving hematoma

DIAGNOSTIC DSA (6/4/10): showed 4.0 x 2.9 x 2.4 mm small nidus in right frontal lobe fed by tiny feeders from anterior internal frontal branch of right ACA. No evidence of AV fistula was seen.

INTERVENTION



Through Rt CFA access, 6F guiding catheter was placed in right ICA. Using 1.2 F magic catheter and 0.008 Mirage wire feeder was selectively catheterised. I ml alcohol was injected. Complete obliteration of nidus was achieved.

Clinical and Radiological follow up showed no evidence of recurrence or any fresh complaints.

Case No 4

HISTORY

This patient presented with complaints of recurrent attacks of GTCS on 12/10/08. Ictus- bimanual automation, gripping of pole with both hands followed by GTCS associated with deviation of angle of mouth, tongue bite, and uprolling of eyes and frothing from mouth lasting for 2-3 minutes. This was followed by a period of loss of consciousness for 10-15 minutes. No post-ictal deficits. No aura. No urinary incontinence.

No history of headache, vomitting, visual disturbances,limb weakness,gait disturbances, bladder and bowel disturbances. No h/o limbweakness, gait disturbances, bladder and bowel disturbances. No h/o visual blurring, diplopia, hearing loss, tinnitus, nasal regurgitation, voice change, or choking sensation while eating.

ON EXAMINATION

Patient conscious, alert with stable vital signs. GCS on admission-15/15.

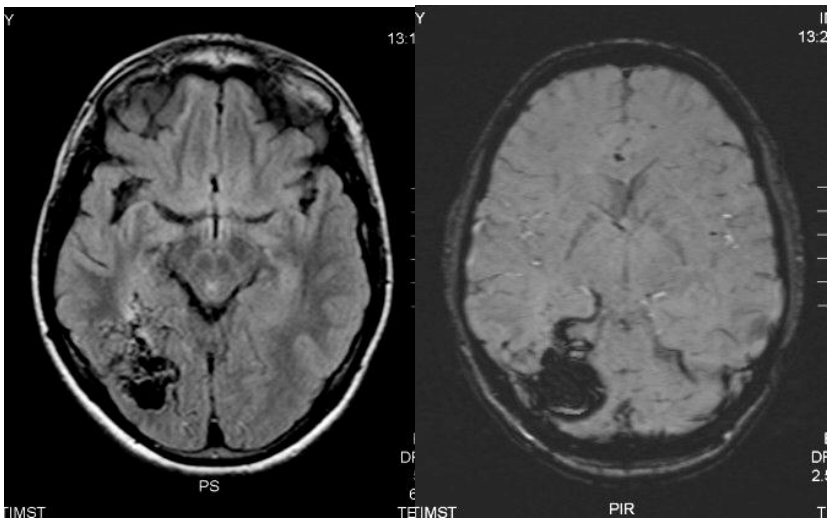
HMF normal. Pupils bilaterally equal and reactive. Extra-ocular movements full. in left eye. Visual fields normal by confrontation. Fundus- no papilledema. No other cranial nerve deficits. Bulk and tone of muscles normal in all 4 limbs. Power grade 5/5 in all 4 limbs. DTRS normal. Plantars flexor. No sensory deficits. No cerebellar signs. Systemic examination unremarkable.

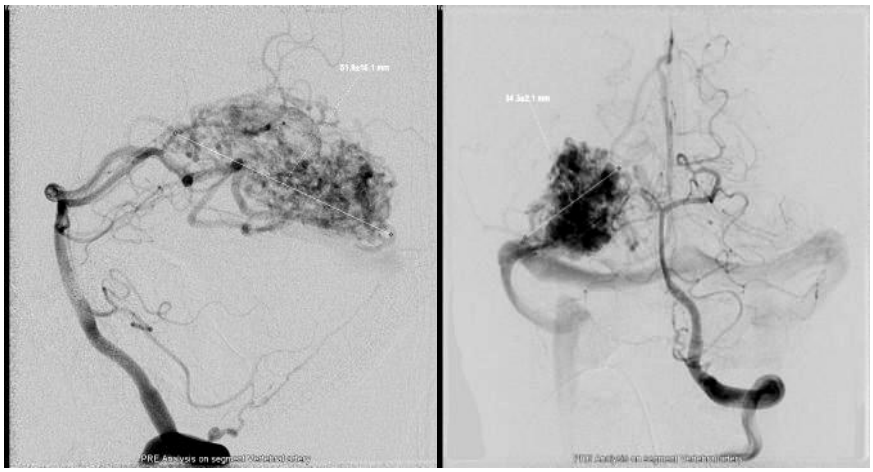
IMAGING

CT Brain : (22/10/08) Right occipital hyperdense serpiginous lesion enhancing well with contrast, draining vein seen.

MRI : (Dec 08) Large abnormal tangle of blood vessels seen in cortex and white matter of right occipital lobe suggestive of AVM nidus

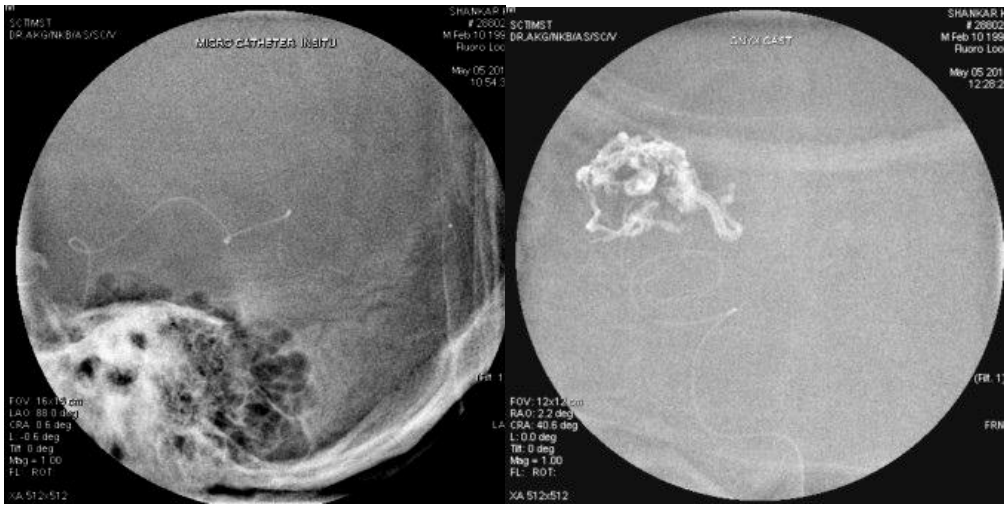
DSA : (05/05/10) compact nidus AVM measring 5.2x3.2x2.2cm in right temporo occipital lobe fed by calcarine branch . Posterior temporal branch of right PCA , temporal branch of right MCA with venous drainage to dilated cortical vein to right transverse sinus. No intranidal/ feeding artery aneurysm.

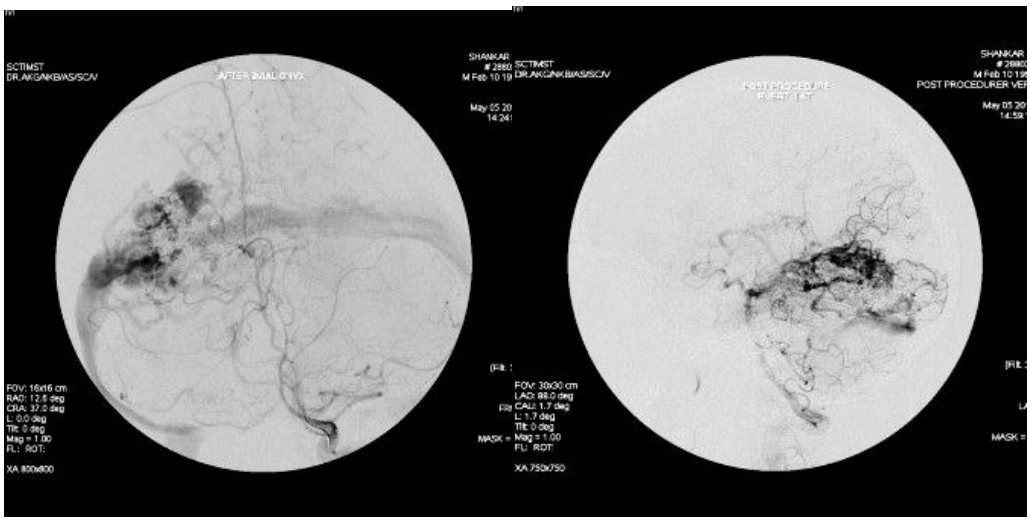




INTERVENTION

FIRST SITTING (05/05/10) : guiding catheter was kept in left v2 segment at c5 body level. marathon microcatheter was taken in calcarine branch of right PCA distally. 2.8 ml of onyx injected slowly over under roadmap guidance, 60 -70% reduction in the size of nidus achieved.



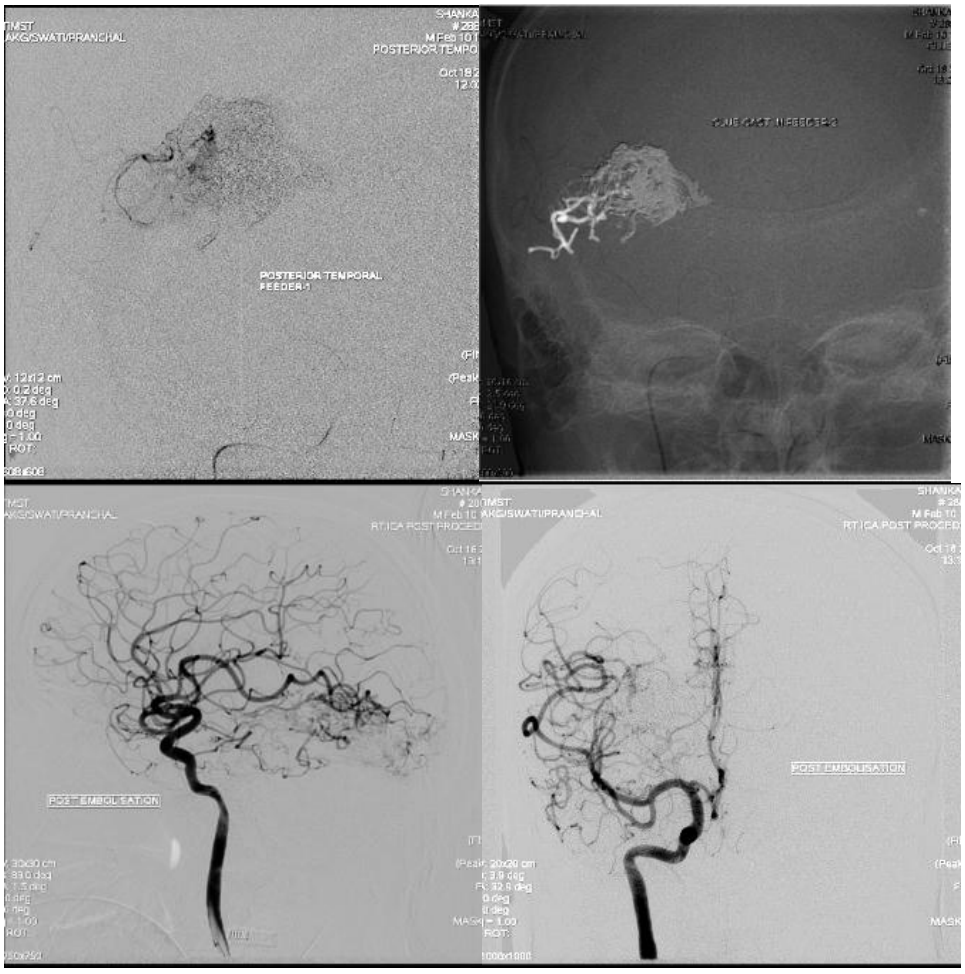


SECOND SITTING (18/10/10):

Posterior temporal branch of right MCA was catheterised with Marathon microcatheter. After getting a safe position in nidus, Onyx was injected but percolation in the nidus was poor. Reflux was noted. Repeated attempt of Onyx was refluxing. After 25 mins, Marathon microcatheter was withdrawn.

This angiogram showed recruitment of meningeal feeders from MMA also. Using Marathon microcatheter, posterior branch of right MMA was catehterised and catheter was passed distally into the nidus and embolized with 1.6 ml Onyx. Check angiogram showed approx 90 - 95 % reduction in the size of the nidus.

Patient was referred for Radiotherapy and is currently on follow up.



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Annexures

Annexure 1: PROFORMA FOR STUDY

(Brain AVMs : Clinicoradiologic spectrum and endovascular management)

I. PERSONAL PARTICULARS

Name **Age** **Sex**

Native place

II. CLINICAL HISTORY

1. **Presenting complaints (**eg seizures/loss of consciousness/ neurodeficit)
2. **Evolution :** Onset , progress and number of episodes
3. **Other relevant neurologic history**
4. **Other relevant history** (past history of significant other illness,family history, treatment history**)**
5. **Clinical findings (**General & systemic examination :especially neurologic examination**)**

III. IMAGING (CT/MRI) FINDINGS

1. **Size & location of lesion.**
2. **Probable arterial feeders and venous drainage**
3. **Associated brain parenchymal changes**

IV. ANGIOGRAPHIC (DSA) FINDINGS

1. **AVM nidus:** size, location, angioarchitecture (diffuse/compact , nidal aneurysms) flow characters (high/low)
2. **Feeders :** Number, parent artery (eg ACA/MCA/PCA), feeding artery ectasia/aneurysms.
3. **Drainage:** Draining veins- location (deep/superficial),number, ectasia/ aneurysmal dilatation.

V. DETAILS OF INTERVENTION

1. **Hardware used (**DSA equipment, post processing**)**
2. **Chief Interventionist details :** number of years of experience, experience in AVM embolization
3. **Technique:** Catheters, microcatheters, Wires used
4. **Agent used:** NBCA/Onyx /other agents

VI. OUTCOME

Immediate

Angiographic
Clinical

Follow up

Angiographic
Clinical

VII. COMPLICATIONS

Immediate
Delayed

VIII. OTHER SALIENT FEATURES (IF ANY)

ANNEXURE 2: MASTER CHART OF THE PATIENTS INCLUDED IN THE STUDY

S No	Age	Sex	Presenting Complaint	Nidus Loc	Embolising Agent	DSA (Nidus obliteration)	Complications
1	17	M	Seizures	Lt frontal	Alcohol 30ml	signifcant	nil
2	45	M	Headache and vomiting	Rt occipital	Alcohol	50%	hematoma with IVH - died
3	28	M	Seizures	Lt frontal	NBCA	40%	Mild facial and limb weaknees
4	13	M	Headache and Vomiting	Rt Callosal	Alcohol 14ml	complete	nil
5	32	F	Seizures	Lt Insular	Alcohol+ NBCA	Partial Reduction	nil
6	34	M	Lt hemiparesis	Lt parietal	NBCA 15%	complete	mild hand grip
7	48	M	Headache and LOC	Rt Cerebellar	Alcohol + 25% NBCA	80% reduction	Nil
8	31	F	Seizures	Lt TP	20% NBCA, Lt PCA feeder	50% reduction	nil
9	41	M	Headache	Lt TP	NBCA - 4 times	small residue	nil
10	36	M	Seizures	Rt TP	22% NBCA, 16ml alcohol	Reduction	nil
11	21	F	Seizures	Lt frontal	17% NBCA	, 95% reduction	hematoma, hemiparesis 1/5
12	20	M	Headache and Vomiting and fall	Lt Thalamic	3ml alcohol and 20% NBCA	70% reduction	nil
13	28	M	Giddiness, Seizures	Lt temporaloral	alcohol 14ml, 13ml	80% reduction	nil
14	36	M	Headache and Vomiting	Lt Parietal	Alcohol, Onyx, NBCA	70% reduction	Ultraflow block
15	37	M	Focal Seizures faceRUL	Lt frontal	Alcohol	40-50% red	focal facial Seizures, stable
16	25	M	Headache and Vomiting, LOC	Rt PO	NBCA & alcohol	complete	nil
17	38	M	headache	Rt PO	NBCA -17-33%	Mild reduction	nil
18	18	M	Seizures	Lt TP	Onyx 5 feeders	70% reduction	Catheter glued
19	52	M	headache	Rt frontal large	Onyx 3ml	60% reduction	focal Seizures, CT SAH with IVH
20	34	M	Seizures	Lt mid frontal	Onyx 1.3ml	Reduction	nil
21	30	F	Seizures jun 07	Rt FP	1.5 ml NBCA, 0.8 ml onyx	40% and 70%	nil
22	44	M	Headache, Rt hemiparesis	Rt Cerebellar	17% NBCA 1.0 & 0.5ml	complete	as desc
23	23	M	speech slurring and Rt hemiparesis	Lt FP	Onyx 1.2ml	signifcant	nil
24	34	M	Seizures	Lt frontal	Onyx	signifcant	Catheter glued
25	13	F	Headache and Vomiting, Seizures	Rt cerebellar	Onyx	signifcant	nil
26	55	M	Headache and Vomiting, LOC	Rt Parietal	NBCA	small reduction	nil
27	29	F	Seizures RUL/LL, 2 ep 2007	Lt PC lobule	3ml onyx, 0.6ml NBCA	complete obliteration	nil

28	23	M	Headache and Vomiting ,LOC	Lt choroidal	1.3ml Onyx	60% reduction	nil
29	15	M	Rec Seizures since 7 yrs age	Lt post basifrontal	Onyx -ml, 0.5 ml	20-30%	extravasn
30	19	F	H&V, 21&22 jun 07	Rt temporaloral	NBCA & 1.0ml onyx	70%	nil
31	42	M	H&V, LOC 20 Jul 07	Lt choroidal	50,22,66% NBCA	90-95% red	nil
32	28	F	H&V, LOC 7	Rt thalmic small	NBCA	95% reduction	nil
33	33	F	GTCS 2 2p 2006-7	small Rt STG	Alcohol 3.0ml	signifcant reduction	nil
34	27	M	LUL Focal Seizures 98	Rt FP	NBCA 33%	50 + 30%	nil
35	49	M	headache	Lt TP	onyx 4.5ml	80%	nil
36	34	M	headache	Lt temporal	onyx 0.5ml	30%	nil
37	25	M	H & LOC 96, 2007	Rt temporal	NBCA - 25-70%	signifcant reduction	nil
38	26	M	Headache and Vomiting Lt hemiparesis	Small Lt frontal ,	0.6ml 17% NBCA	complete obliteration	nil
39	37	M	Headache	Lt post frontoparital	12ml alc inf parietal, 1ml 20% NBCA pericall	small residual	nil
40	23	M	Headache	Rt temporal	NBCA	partial rd	nil
41	37	M	Headache & LOC, Lt hemiparesis	Rt TPO	NBCA	signifcant	nil
42	22	M	Headache & Nausea	Rt occipital	NBCA 20%	40% red	nil
43	26	M	Headache and Vomiting, Ac Lt hemiparesis	Rt parietal	NBCA 17%	Total ob	nil
44	34	F	Headache, LOC,Lt hemiparesis	Rt temporal	Onyx 18	partial rd	Ultraflow broke , pushed to ECA.
45	13	M	Headache	Lt post frontal	Onyx 18 2.0ml	25% , 40, near comp	check dsa 2009 - 5% residual
46	34	M	Seizures since 17 yrs age	Rt temporal	Onyx 2.8ml	80%	Catheter gluing, cut at groin
47	27	M	headache	Lt Ociciptal	Onyx 4.0ml	complete obliteration	Catheter gluing, cut at groin
48	48	M	Headache & Vomiting, LOC	Rt Parietal	Onyx 0.6ml	complete obliteration	Catheter gluing, cut at groin
49	24	F	Headache and Vomiting, LOC	Rt post temporal	Onyx 0.4 ml	complete	nil
50	20	M	headache	Lt frontal	Onyx 1.5ml	90%	nil
51	13	M	Headache & Vomiting, LOC	Rt frontal large	Alcohol 1ml	complete	nil
79	11	M	Headache & LOC	Rt cerebellar	NBCA, Onyx	50%	nil
53	44	M	Headache & LOC	Lt parietal	20% NBCA	40%	wire induced CCF

54	17	M	Seizures 4episodes	Rt Inf parietal	Onyx 1.5ml	95%	nil
55	43	M	Severe Headache, Seizures	Lt PO	80% NBCA, 1.2ml	partial	nil
56	43	M	Headache & Seizures	Rt cerebellar	Onyx 10.0 ml, alcohol	80%	nil
57	11	F	Seizures 4episodes	Rt Frontal	Onyx 0.2 n 0.4ml	partial	nil
58	20	M	Seizures 4episodes	Lt Parietal	Onyx 0.2ml	10-20%	nil
59	51	F	twice LOC	Lt PO	Onyx 1.0 ml	90%	nil
60	42	M	Hemiparesis	Rt Frontal	Onyx 0.5ml	complete	nil
61	42	F	numbness Lt half of body	Lt temporal	Onyx 1.6ml	complete	nil
62	30	M	Seizures 10 ep	Lt Parietal	17% NBCA	complete	nil
63	14	M	Seizures	Rt Occipital	Onyxl, NBCA	70 & 90%	nil
64	51	M	Headache & hemiparesis	Lt frontal	Onyx 3.4ml	70%	Catheter gluing, cut at groin
65	55	M	GTCS- 5-6 episodes	Rt frontal	Onyx 0.2ml	10-20%	nil
66	56	M	headache	Rt cerebellar	Onyx 1.1ml	80%	Lat medullary infarct, Catheter gluing
80	40	M	Rt facial neuralgIa	Rt cerebellar	Onyx, 0.2 ml	10% red	nil
67	18	M	Occipital Seizures	Rt occipital	Onyx, attempt	60%	contrast extracsn, spont sealed
69	14	M	Seizures, Tr Lt hemip	Rt post cingulate	Onyx 0.4ml	90-95%	nil
70	33	M	GTCS .	Rt PO	Onyx (avm), NBCA	50-60%	GTCS post procedure
71	55	M	LOC	Lt PO	Onyx (0.8ml)	60-70%	GTCS post procedure
72	20	F	Headacehe and vomiting, LOC	Lt PC lobule	Onyx 1.0ml	complete	nil
73	54	M	Headache & GTCS	Lt PO	Onyx 6ml	90%	nil
74	15	M	Headache and Vomiting, Rt hemip	Rt cerebellar	Onyx 1.0ml	30%	catheter gluing, broke in aorta
75	10	M	Headacehe and vomiting	Rt cerebellar	Onyx 4ml	50%	nil
76	36	F	Headacehe and vomiting	Rt temporal	Onyx	70%	SAH , resolved
77	19	F	headache & Seizures	Rt frontal	Onyx	10%	extravasn, sealed with 20% glue
78	10	F	Headache,Uncosciousness	Lt TP	Onyx	60%	nil