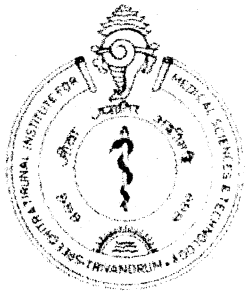

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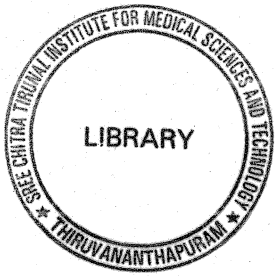

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CERTIFICATE

This is to certify that the dissertation entitled **"Brainstem Cavernomas – Experience with 25 patients"** has been carried out by GULZAR GUPTA at Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram for the award of M.Ch. degree in Neurosurgery.

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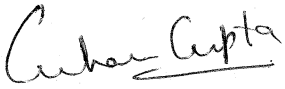

GULZAR GUPTA

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INTRODUCTION

Cavernous Malformations of the central nervous system affect 0.4 to 0.9% of the population and account for 5 to 10% of all central nervous system vascular malformations[1,2]. Brain stem Cavernous Malformations account for 9 to 35% of all Cavernous Malformations[1,3]. Unlike supratentorial brain stem cavernomas, literature on brain stem cavernoma is sparse probably because before the era of magnetic resonance imaging, cavernous malformations of the brainstem were only diagnosed with certainty at autopsy or at surgery. With the advent of magnetic resonance imaging, however, cavernomas have been diagnosed with increasing frequency. In the realm of intrinsic brainstem lesions, brainstem cavernous malformations are ideal lesions to resect. They are histologically benign and contain no neural tissue. If removed completely, they are one of the few curable brainstem tumors. The successful and safe resection of these lesions, however, did not become routine until skull base and frameless sterotactic techniques were developed. In 1953, Teilmann reviewed the 46 cases of vascular malformations of the pons that had been reported in the literature up to that time.[4] During the next half century, numerous authors resected these lesions, with good results.[5-25]

Their natural history remains poorly understood, with only small surgical series reported in the literature. Decision-making regarding the treatment of patients with brainstem cavernomas with or without previous hemorrhage remains controversial. We reviewed the cases of 25 patients with brain stem cavernomas both operated and not operated to provide a more detailed analysis of the natural history, radiographic features, surgical challenges and outcome involving these complex lesions.

MATERIALS AND METHODS

This study involved a retropsective analysis of the case records and radiological images of all the patients diagnosed and treated for a brain stem cavernomas in our institute since 1980.

All patients presented with clinical and radiological signs of one or multiple brainstem hemorrhages. Diagnostic workup included multiplanar magnetic resonance imaging studies and computerized tomography scanning in all cases. Angiography was also performed in selected cases.

Surgical management

Keeping in line with the evolving trends our policy towards brain stem cavernomas has evolved from one of essentially conservative management to radical excision whenever possible. We had fifteen patients in the surgical group. A cavernoma considered for surgical resection satisfied at least one of the following criteria.

1) it abutted the pial surface or was exophytic
2) it produced repeated hemorrhages causing progressive neurological deficits
3) there was acute hemorrhage with significant mass effect produced by a large intralesional hemorrhage.

The goals of surgery were to achieve complete extirpation of the lesion to prevent rebleeding, to minimize damage to the surrounding normal brainstem parenchyma, and to

preserve associated venous anomalies. No attempt was made to remove hemosiderin-stained tissue. The diagnosis of all resected lesions were confirmed by histological examination.

Conservative management

A conservative line of management was adopted when

a) Medical contraindications for surgery
b) Single bleed from which the patient has recovered and imaging shows a small deep seated cavernomas
c) The patient refused surgery on being informed about the risks associated with surgery

We had ten patients who were treated conservatively due to either of the above reasons.

A comparative study was done to

a) Factors influencing long term outcome in patients with brain stem cavernomas treated either conservatively or by surgical excision.
b) Factors influencing outcome among patients with brain stem cavernomas treated by surgical excision.

The following parameters were analyzed:

1) number of preoperative hemorrhages;
2) location of the cavernous angioma (midbrain, pons, pontomesecephalic, pontomedullary, medullary / cervicomedullary);
3) Pre-and post operative neurological status

4) Distance from the brain stem surface of the cavernous angiomas.

5) timing of surgery with relation to the bleed.

The same was compared with those ten patients who were not operated due to various reasons.

REVIEW OF LITERATURE

Cavernous angiomas belong to a group of intracranial vascular malformations that are developmental malformations of the vascular bed. These congenital abnormal vascular connections frequently enlarge over time. The lesions can occur on a familial basis. Patients may be asymptomatic, although they often present with headaches, seizures, or small parenchymal hemorrhages. As a cause of hemorrhage, cavernous angiomas are far less common than hypertension; nevertheless, as a cause of hemorrhage, they must be excluded, especially in young patients. Cavernous angiomas can also cause a variety of symptoms and neurologic findings similar to those of tumors. Cavernous malformations are most commonly found in the cerebral cortex, although they may also occur in the brainstem, spinal cord, retina, cranial nerves, and cerebral ventricles.[17, 26, 27]

Types of vascular malformations

Types of vascular malformations are differentiated from one another on the basis of their gross and histopathologic characteristics.

Traditionally, intracranial vascular malformations are grouped into 4 types[28] as follows:

- Capillary malformations (or telangiectasias)
- Cavernous malformations (cavernous angiomas / hemangiomas)

- Venous malformations
    - Venous angiomas
    - Vein of Galen malformations
    - Venous varix
- Arteriovenous shunting malformations
    - Parenchymal malformations
    - Dural arteriovenous shunting malformations (arteriovenous malformations [AVMs]) and arteriovenous fistulae
    - Mixed pial-dural arteriovenous malformations

Newer schemes add the following 2 classifications:

- Arterial malformations (no arteriovenous shunting)
    - Congenital angiodysplasias
    - Intracranial aneurysms (berry/saccular, giant, serpentine)
- Mixed malformations
    - Venous cavernous type
    - Arteriovenous malformation venous type
    - Cavernous arteriovenous malformation type

The evolution of such classification schemes has paralleled that for vascular anomalies in other organ systems. Classification based solely on descriptive terminology has given way to more precise pathoanatomic and embryologic definitions.

Pathophysiology

Grossly, cavernous angiomas are typically discrete multilobulated lesions that contain hemorrhage in various stages of evolution. Because they are lobulated and dark red to blue, the lesions grossly resemble small mulberries. The histoarchitecture of the component vessels resembles that of capillary telangiectasias, consisting of a single layer of endothelium and differing quantities of subendothelial fibrous stroma, with distinct absence of smooth muscle and elastic fibers. The immaturity of the blood vessels within the cavernous angioma differentiates it from a venous angioma, which conversely consists of mature vessels responsible for normal venous drainage.

Cavernous angiomas are considered to be congenital vascular hamartomas composed of closely approximated endothelial-lined sinusoidal collections without significant amounts of interspersed neural tissue. The lack of intervening neural tissue is the only histopathologic characteristic that distinguishes these lesions from capillary telangiectasias. As a result, some authors have suggested that these lesions actually represent a phenotypic spectrum within a single pathologic entity. Nearly all cavernous malformations show evidence of recent and remote hemorrhage, as suggested by the presence of hemosiderin-laden macrophages, cholesterol crystals, and hemosiderin-stained parenchymal tissues. Clots and blood products of

various stages of evolution within the lesion, as well as calcification and gliosis, often are seen. The lesions surround the cavernoma, creating the appearance of a pseudocapsule. Electron microscopy analyses have implicated defective endothelial tight junctions as a potential explanation for the propensity for hemorrhage seen in these lesions. [29, 30]

Cavernous angiomas develop embryologically from malformed capillaries of the intraneural vascular territory that slowly enlarge and undergo obliteration and progressive fibrosis; gliosis of the interposed nervous tissue results in its complete destruction. Thus, the cavernoma develops in the final arrangement of the partially or completely thrombosed vascular malformation without interposed nervous tissue.

Associated venous anomalies may induce the formation of cavernous malformations and play a role in their recurrence. It has been postulated that abnormal hemodynamics of venous malformations might induce the formation of cavernous malformations. Awad, et al.[31] suggested that the abnormal vascular beds of developmental venous anomalies may induce hemodynamic disturbance (venous hypertension) or may be fragile enough to cause microhemorrhage that in turn might cause reactive angiogenesis with new vessel formation and coalescence. Such a process has been described as "hemorrhagic angiogenic proliferation." Alternatively, Developmental

venous anomalies-related venous outflow restriction and venous overload may open preexisting arteriovenous connections, resulting in tiny arteriovenous fistulas that can enlarge over time.[32] Finally, it has been suggested that chronically increased intraluminal pressure and resultant reduced tissue perfusion leading to tissue hypoxia may stimulate a local increase in angiogenic factors inducing the formation of vascular malformations.

There are several lines of evidence that argue for a neoplastic basis for cavernomas. Although much of the dynamic behavior of these lesions can be explained by hemorrhage and hemorrhage resolution, less common behaviors such as de novo cavernoma formation and increases in lesion size in the absence of clinical hemorrhage suggest a neoplastic process. As cavernomas are composed almost exclusively of endothelial cells embedded in a collagenous matrix, this growth would likely represent a clonal expansion of endothelium. Other reported observations that support this argument include seeding of a cavernoma along a biopsy track,[33] appearance of a new lesion under the hormonal influence of pregnancy,[34] appearance of cavernomas in fields of previous radiation[35] and the presence of proliferating cell nuclear antigen in endothelial cells in cavernomas.[36]

The identification of KRIT1 mutations in a subset of patients with cavernomas[37, 38] suggests a molecular basis for

the neoplastic expansion of endothelial cells. The KRIT1 was cloned by virtue of its interaction with Rap1A, a small ras family guanine triphosphatase thought to function as an antagonist of ras.[39] If KRIT1 (in conjunction with Rap1A) functions as a tumor suppressor by antagonizing ras function, then its mutation might lead to unchecked or disordered growth of endothelial cells giving rise to a cavernoma.

Genetics

Genetic factors have been identified in 20 to 30% of patients with Cavernous malformations.[40,41] Familial cases are often characterized by the presence of multiple lesions, whereas sporadic cases usually entail only a single malformation. These cases exhibit an autosomal dominant pattern of inheritance and seem to affect the Hispanic population in particular. Recent research has demonstrated at least 3 separate genes related to the familial form of the disease.[42, 43, 44] Two of these genes have been precisely located. Current research is ongoing to more precisely locate the third. The first gene is called *cerebral cavernous malformation1* and is located on chromosome 7 at band 7q11.2-q21. It is also known as KRIT1, for the protein created by the gene. Of familial cavernous angiomas, 40% can be linked to a *cerebral cavernous malformation1* genetic mutation. This is the gene responsible for most of the cases of familial multiple cavernous angioma in Mexican-American

families and in a number of other families. *Cerebral cavernous malformation1,* the *KRIT1* gene, is responsible for creating KRIT1 protein, or Krev interaction-trapped 1 protein. The exact function of KRIT1 protein is not known. If both copies of the *cerebral cavernous malformation1* gene mutate, the KRIT1 protein cannot function and cavernous angiomas form. The second gene is called *cerebral cavernous malformation2.* It is located at band 7p15-p13 and controls the production of a protein named malcavernin. Of familial cavernous angiomas, 20% can be linked to a cerebral *cavernous malformation2* mutation. The third gene (*Cerebral cavernous malformation3*) identified as linked to familial cavernous angioma is on chromosome 3 at band 3q. Research is ongoing to further delineate the function of this gene and its relationship to cavernous angiomas.

Although the biological progression of cavernous angiomas is well recognized, the mechanisms of enlargement and growth are still being debated. Mechanisms of the malformation enlargement are well defined, and they include the following: 1) progressive ectasia of the vascular channels; 2) thrombosis of the contiguous vascular channels with fibrosis; 3) peripheral blood collections undergoing connective organization; and 4) formation of peripheral cysts resulting from internal hemorrhage. In some reports[45] however, investigators have suggested a role for proliferative mechanisms in the enlargement and growth of cavernous

angiomas. These mechanisms include endothelial proliferation and neoangiogenesis, which are regulated by growth factors and ECM proteins. Some recent immunohistochemical studies have shown expression of both proliferative indices and angiogenic and growth factors in brain cavernomas. [36, 46]

Incidence:-

With the advent of magnetic resonance imaging, cavernous angiomas are currently the most commonly identified brain vascular malformations. In early studies of major autopsy reports, the calculated prevalence was 0.02-0.53%. Magnetic resonance imaging of lesions with the appearance of cavernous hemangiomas provided information that led to a prevalence of 0.39-0.9%. The detection of previously unidentified asymptomatic lesions by using magnetic resonance imaging has recently raised the estimated overall prevalence to 0.45-0.9%.

Multiple lesions are seen in approximately 15-33% of spontaneous cases, although one series reported an incidence as high as 50%. A familial form of the disorder exists and is inherited as an autosomal dominant trait with variable expression. Multiple lesions are more common in the familial form, occurring in as many as 73% of patients. Cavernous angiomas also appear to be the most common CNS vascular malformation subtype in patients with mixed lesions. The most common combination includes venous

malformations, which are identified in approximately 10-30% of patients with cavernous angiomas.

Presentation:-

Not all cavernous angiomas are associated with symptoms, but once patients become symptomatic, 40-50% present with seizures, 20% present with focal neurologic deficits, and 10-25% present with hemorrhage. Symptoms may progress rapidly, be stable for years; or wax and wane, as in multiple sclerosis.[47]

Patients often present with only a headache, but the reliability of headache as a presenting symptom and etiology remains controversial. Headaches are estimated to be a relevant symptom in as many as 25% of patients. Acute headaches may result from parenchymal irritation secondary to gross or repeated extralesional hemorrhage. Chronic headaches are believed to be the result of mass effect in slow-growing larger lesions as a result of repeated intralesional hemorrhage.

Cavernous angiomas can bleed in a number of different ways:

- Angiomas can bleed slowly within the walls of the angioma and remain quite small. However, continued small hemorrhages in the same cavernous angioma often cause deterioration in function.

- Angiomas can bleed more profusely within the walls of the angioma. This can cause them to grow and put pressure on the surrounding brain tissue.
- Finally, angiomas may bleed through a weak spot in the angioma wall into the surrounding brain tissue. This is called an overt hemorrhage.

The clinical consequences of hemorrhage vary such that location becomes important. Small hemorrhages in critical locations can have more severe effects, and thus, they are more likely to produce symptoms (eg, brainstem involvement). Progressive neurologic deficits are more often associated with cavernomas in the infratentorial space and with lesions that demonstrate slow enlargement because of rebleeding episodes.

Natural history

Cavernous angiomas can occur at any age, but they are most likely to become clinically apparent in patients aged 20-40 years.Cavernous angiomas can be found in any part of the brain because they can occur at any location along the vascular bed. Frontal and temporal lobes are the most common sites of occurrence, and 80-90% of the lesions are supratentorial. The deep cerebral white matter, corticomedullary junction, and basal ganglia are common supratentorial sites, whereas the pons and cerebellar hemispheres are common posterior fossa sites. Intracranial extracerebral cavernous angiomas also occur, but these are

less common. They typically occur in the middle cranial fossa and originate from the cavernous sinus. Cavernous angiomas also can occur in the spinal cord, where they frequently coexist with multiple brain lesions.

The risk of hemorrhage is not well established, but it is estimated to be 0.2-2% per lesion per year (Table 1). Incidental lesions and those discovered during the evaluation of nonspecific symptoms, such as headache, have a low risk of symptomatic hemorrhage ranging from 0.1[6] to 0.6%[48] per patient per year. A more aggressive behavior has been observed in younger patients,[49] females[17] and in patients who have suffered previous hemorrhage. Authors of several reports have suggested that the cavernous malformations associated with a developmental venous anomalies have a more aggressive clinical course.[50]

The pathophysiological basis of such a more aggressive clinical course is largely unknown. The lesions do not usually produce life-threatening hemorrhages because most hemorrhages associated with the lesions are small and of low pressure. The effects usually result from the location of the lesion and, at times, their slow expansion.

TABLE – 1 Natural History of Cavernous Malformations

Author, Year	Rate of symptomatic hemorrhage	Comments
Del Curling et al,[6] 1991	0.1% per lesion/year	Retrospective study based on patients' historical recall of hemorrhagic events. Assumed all lesions were present from birth
Robinson et al,[51] 1991	0.7% per lesion/year	Prospective study
Zabramski et al,[52] 1994	1.2% per lesion/year	Prospective magnetic resonance imaging study of patients with familial form of this disease. Overall rate of hemorrhage was 2.1% per lesion/year, but only 60% of episodes were symptomatic.
Kondziolka et al,[48] 1995	1.3%/year(retrospective) 2.6%/year	Found that rate of hemorrhage was significantly lower in

	(prospective) 0.6%/year (incidental) 4.5%/year (symptomatic)	patients presenting with incidental lesions compared with those with a previous history of symptomatic hemorrhage
Aiba et al,[17] 1995	0%/year (incidental) 0.4%/year (seizures) 22.3%/year	Prospective study. Found rate of hemorrhage was related to presentation; low in those presenting with seizures or (gross hemorrhage) incidental lesions; high after gross hemorrhage into the surrounding brain.
Porter et al,[53] 1997	4.2%/year	Based on retrospective review from time of first symptomatic hemorrhage. Rate is remarkably similar to that reported for symptomatic lesions by Kondziolka et al[59]

Infratentorial location and previous gross hemorrhage are associated with increased risk of subsequent and progressive neurologic disability. When large enough, the hemorrhages can cause both obstructive and nonobstructive hydrocephalus.

Associated Venous Anomalies

Venous anomalies were defined by abnormal veins found in the resection bed of the cavernous malformation. The anomalies may be large enough to be identified radiographically and have a "ca-put medusa" appearance, or they may be radiographically occult and discovered only during intraoperative inspection. In previous studies, venous malformations have been reported to be associated with cavernous malformations of the brainstem 8 to 26% of the time[8, 54]. Later, Fritschi, et al[55], in an extensive review of the literature, reported an incidence of approximately 8% of venous anomalies accompanying cavernomas. The 100% association of cavernous malformations with venous anomalies in Porter's series represent a significant new report in the pathophysiology of these lesions. In the same series preoperative magnetic resonance imaging findings were consistent with the "classic" developmental venous anomalies appearance on 32% of 73 preoperative magnetic resonance images and in 14% of 50 angiographic studies. This observation suggests that the prevalence of associated developmental venous anomalies may be underestimated

even when high-field magnetic resonance imaging is used, because small venous anomalies not visible on preoperative studies may be noticed in the surgical cavity following resection of the cavernous malformations. It has been suggested that latent venous hypertension in association with venous anomalies can predispose Cavernous malformations to hemorrhage. In 1999, Abdulrauf, et al.[56] conducted a retrospective analysis of 55 consecutive patients with cavernous malformations and found that 38% of those with cavernous malformations alone presented with hemorrhage as opposed to 62% of those who harbored cavernous malformations associated with developmental venous anomalies. These venous anomalies perform the critical function of draining the normal brain and must be preserved when cavernous malformations are resected. If the main trunk is sacrificed, devastating venous infarction can result.

It cannot be excluded that by treating the cavernous malformation we are treating the result of the so-called "hemorrhagic angiogenic proliferation" and not the disease itself, which may indeed be the developmental venous anomalies.

Cerebral cavernous malformations and epilepsy

Cerebral cavernous malformations are malformed blood vessels and do not typically include functioning neural tissue. Hence they are not intrinsically epileptogenic, but they

can induce seizures through their effect on the surrounding brain tissue. These effects may include ischemia, venous hypertension, gliosis, deposits of blood breakdown products, and cellular and humoral inflammatory responses. Epilepsy in association with cerebral cavernous malformations has been shown to induce different firing patterns in adjacent hippocampal tissue slices than epilepsy associated with neoplasia.[58] Overt hemorrhage from cerebral cavernous malformations may create encephalomalacia and cortical scars that may be independently epileptogenic. These sequelae are often observed on magnetic resonance imaging and may be associated with focal neurological deficits. Chronic deposition of blood breakdown products is characteristic of cerebral cavernous malformations, and gliotic hemosiderin-stained brain tissue adjacent to the lesions is thought to be a source of epileptogenic activity. Patients with cerebral cavernous malformations in cortical locations are subject to a prospective lifetime risk of new seizures. This risk is greatest with cerebral cavernous malformations situated in temporal, frontal, and perilimbic locations.

Resection of vascular malformations may be undertaken to prevent future hemorrhage and/or for seizure control. Lesionectomy is associated with excellent postoperative seizure control in many patients.[59] The likelihood of postoperative seizure control following simple

lesion excision is greater in patients with less intractable preoperative epilepsy and also in patients with extratemporal lesions. Unlike temporal lobectomy, there are no anatomically standard operations for performing a simple lesionectomy. The procedures are divided into temporal lesionectomies and extratemporal lesionectomies. In patients with temporal lesions and intractable epilepsy, studies in which a simple lesionectomy was performed without resection of mesial structures showed a low seizure control rate ranging from 20 to 45%. [60,61]

In cases of extratemporal lesional epilepsy, lesion resection alone has provided favorable results, with seizure control rates varying from 65 to 95%.[60] Of patients who harbor a single cerebral cavernous malformation, undergo lesionectomy for treatment of recent-onset, localization-related seizures, and are seizure free postoperatively, up to half may successfully taper off all anticonvulsant medications.[62, 63] Several studies have shown that complete lesion excision is necessary for seizure control in the majority of patients who harbor a cerebral cavernous malformation that has been shown to be responsible for their seizures.[79] It also is well documented that lesion excision alone may not always suffice for seizure control, especially in patients with truly intractable epilepsy. Many patients who have had persistent intractable seizures following lesion excision have had lesions in the temporal lobe. [59]

Some of these patients became seizure free after additional resection of epileptogenic brain tissue in the same region. Overall analysis of the published outcome data demonstrates symptom improvement in the majority patients with intractable epilepsy.[6, 51] Among patients treated with surgical resection of the offending lesion, 50 to 90% were seizure free postoperatively with or without anticonvulsant therapy.

An issue that must be considered is the possibility that the cerebral cavernous malformation identified on imaging may represent an incidental finding and may not play any role in seizure onset. This may be the situation in up to 6% of cases of patients with cavernous angiomas and epilepsy.[64]

A management algorithm to deal with supratentorial cavernomas, taking into account clinical presentation, lesion location, and genetic findings is recommended. The algorithm is as follows[65].

1. Asymptomatic cerebral cavernous malformations are generally observed carefully, with follow-up magnetic resonance imaging performed at yearly or 2-year intervals.
2. Symptomatic (severe headache, seizures, progressive neurological deficits) cerebral cavernous malformations in noneloquent areas should be resected with the aid of frameless stereotactic guidance. In eloquent and/or deep locations, symptomatic (intractable seizures, severe or

repeated hemorrhage, progressive neurological deficits) cerebral cavernous malformations should be resected with the aid of frameless stereotaxy and integrated magnetic resonance imaging studies.

3. In cases of cerebral cavernous malformations presenting with seizure, the threshold for intervention depends on lesion accessibility, eloquent location, and severity of the seizure disorder as well as drug resistance. Patients with multiple cavernous malformations should be studied extensively to decide if one or more lesions are responsible for the symptoms. In noneloquent and accessible areas, surgery should be performed to remove the lesion as soon as possible after the seizure disorder begins. In cases of temporal lobe seizures, if simple lesionectomy fails to correct the disorder, detailed cortical and electrode electroencephalographic mapping should be performed, possibly followed by epilepsy surgery (such as amygdalohippocampectomy).
4. Associated venous anomalies should be spared during surgery for cerebral cavernous malformations.
5. In suspected familial cases identified based on clinical and/or neuroimaging results, genetic analysis must be performed. In the event of positive findings on mutational analysis, the genetic study should be extended to family members, who could benefit in two ways: 1) in the event that a mutation carrier is found, by early detection of

cerebral cavernous malformations; and 2) in the event that no mutation is found, by exclusion of the family member from the at-risk group. Clinical and neuroimaging monitoring should be recommended also in cases of negative findings on mutational analysis but suspicious clinical symptoms or a known family history of the disorder. When the family history is not available or is unreliable, genetic analysis should also be considered in patients harboring an apparently single, sporadic lesion to detect cryptic or de novo genetic mutation.

6. In cases of incomplete resection, repeated surgery is advocated for cerebral cavernous malformations located in noneloquent areas, whereas in a deep and/or eloquent location, further surgery should be performed on a case-by-case basis.
7. Long-term follow-up imaging in all patients to detect recurrences or de novo lesions is recommended

Brain stem cavernomas

In the first half of the 20th century, brainstem surgery was guided by ventriculography. In 1851, Virchow reported the first case of a brainstem hemangioma, and more than a century later, Russell coined the term cryptic vascular malformation to classify these lesions as distinct entities[66]. Not until the discovery of computed tomography, were major strides in imaging the brainstem made. The first surgery for brain stem cavernomas was performed by Dandy in 1928.

Since that time approximately 300 cases of brainstem cavernomas have been reported in the literature.[2, 13, 67-70] (Table2).

Table 2: Summary of the large series of brainstem cavernomas published

		Surgery	Conservative
Fahlbusch et al	1991	10	10
Fritschi et al	1994	16	08
Sathi et al	1996	23	27
Amin hanjani et al	1998	14	00
Cantore et al	1999	12	—
Steinberg et al	2000	42	—
Porter et al	2001	36	—
T. Mathiesen et al	2003	29	39
Chung-cheng wang	2004	15	10

Natural History

Brain stem Cavernous Malformations account for 9 to 35% of all Cavernous Malformations[1,3] Few large clinical series of brainstem cavernous malformations exist, and fewer than 300 cases have been reported.[11, 15, 22, 24, 25, 55] Thus, their natural history remains poorly defined. Brainstem cavernous malformations may be found incidentally, or they can manifest with severe neurological deficits.[55] Patients with cavernous malformations may be relatively asymptomatic or they may be neurologically devastated. Hemorrhage from

brainstem lesions may be more likely to elicit symptoms than hemorrhage from lesions of similar size in other locations (for example, cerebral hemisphere) because of the relatively larger number of the critical tracts and nuclei in this region.

Although histologically benign, brainstem cavernous malformations can cause devastating neurological consequences or death. The most common symptoms, however, include multiple neurological deficits, depending on the presence of an expanding hemorrhage or the lesion's location. Constitutional symptoms such as headache, nausea and vomiting are also common. Hemorrhage usually causes acute onset of symptoms, but slowly expansible lesions may cause neurological deficits to worsen gradually. Clinically, these patients may appear to have brainstem stroke, tumor or infection. Alternatively, the waxing and waning of the symptoms can mimic multiple sclerosis.

Kondziolka and coworkers[48] reported prospective hemorrhage and rehemorrhage rates of 2.4% and 5% per year, respectively. The timing of a subsequent hemorrhage, however, is impossible to predict. The interval between hemorrhages has ranged from hours to 17 years.[25] With each hemorrhage, symptoms tend to worsen and then improve, but less so after each incident. After one hemorrhage, the likelihood of a subsequent hemorrhage is substantially higher than in patients with silent lesions. [9, 17, 48, 55]. Further, the lesion's location appears to affect the risk of

symptomatic hemorrhage; the hemorrhage rate of infratentorial lesions may be 30 times that of lesions in the supratentorial compartment.[53]

Robinsons and colleagues[51] prospectively followed 57 patients for an average of 26 months and found a risk of symptomatic hemorrhage of 0.7% per lesion per year. This rate compares favorably with the risk of symptomatic hemorrhage reported by Zabramski and associates[52] in a group of patients with familial cavernous malformations; 21 patients with 128 Magnetic Resonance Imaging - documented cavernous malformations were followed for an average of 2.2 years. Serial Magnetic Resonance Imaging studies and follow-up examinations at 6 to 12 month intervals documented hemorrhage in six lesions, for an overall rate of hemorrhage of 2.1% per lesion per year. Three of the six hemorrhages were clinically symptomatic, for a symptomatic hemorrhage rate of 1.2% per lesion per year.

Kondziolka and colleagues[48] reported a slightly higher hemorrhage rate of 2.6% per year but noted that the risk of hemorrhage was related strongly to clinical presentation. They followed 122 patients with cavernous malformations and found that the hemorrhage rate was significantly lower in patients who presented with incidental lesions: 0.6% per year compared with 4.5% per year in patients with a history of previous symptomatic hemorrhage. Aiba and associates[17] followed 110 patients with cavernous malformations for a

mean of 4.5 years and reported a 0% hemorrhage rate for patients with incidental lesions versus 0.4% per year in patients who presented with seizures.

Porter and colleagues[25] reported an overall annual event rate of 4.2%. An *event* referred to neurological deterioration with or without radiologically proven hemorrhage. Location was the most important factor for predicting future events, with significantly higher rates for deeply located lesions (10.6% per year) compared with superficially located lesions (0% per year).

Hemorrhage rates appear to be particularly high in patients who present after bleeding episodes that violate the lesion capsule, producing a gross extralesional hemorrhage into the surrounding brain. In this select group of patients, Aiba and associates[17] found a 22.3% per year rate of recurrent symptomatic hemorrhage. Similar rebleeding rates have been reported after incomplete resection of cavernous malformations.[55,71,72]

The risk of permanent neurological deficits caused by hemorrhage is related directly to the location of the lesion. Focal neurological deficits and death are associated almost exclusively with hemorrhage into lesions located in the brainstem or basal ganglia. Subcortical lesions rarely reach sufficient size to produce neurological deficits secondary to mass effect. Seizures are a significant cause of morbidity in patients with subcortical lesions.

Radiology

Before the introduction of modern imaging technology, cavernous malformations were considered rare lesions. In 1976, Voigt and Yasargil[73] described their clinical experience with one case and thoroughly reviewed the world literature, finding only 126 reported cases. Soon after the publication of this article, Computed Tomography became widely available. Although Computed Tomography was a significant step forward in neuroimaging, it lacked sensitivity and specificity for the diagnosis and imaging of cavernous malformations. Only partially calcified or recently hemorrhagic lesions could be visualized readily, and diagnosis required pathologic confirmation.

Nonenhanced computed tomography scans demonstrate cavernomas as focal oval or nodular-appearing lesions that demonstrate mild-to-moderate increased attenuation, without mass effect on the surrounding brain parenchyma. Areas of calcification and hemosiderin deposits in the walls of the fibrous septa, combined with the increased blood pool within the lesion, are responsible for hyperattenuation on nonenhanced images. computed tomography scans demonstrate calcifications in as many as 33% of cavernomas. If the lesions are older, they can contain central hypoattenuating nonenhancing areas, which correspond to cystic cavities from resorbed hematomas.

Contrast enhancement can vary from minimal to striking, although 70-94% of cavernous malformations demonstrate mild-to-moderate enhancement after the intravenous administration of contrast agent. In large part, this enhancement results from the increased blood pool within the vascular component. The slightly heterogeneous and mottled enhancement results from the fibrous intravascular septa, and the peripheral rim of decreased attenuation results from the pseudocapsule of gliotic tissue surrounding the lesion.

Mass effect is not common unless the lesion is associated with recent hemorrhage. Cavernomas may not be detected when they present as acute intracerebral hematomas on nonenhanced computed tomography images. After the administration of contrast material, cavernomas may be identified as areas of nodular enhancement adjacent to the hematoma.[74] Although cavernous angiomas may be apparent and although they can be diagnosed by using computed tomography scans, computed tomography is not the imaging modality of choice. Computed tomography has only a limited role in the diagnosis of cavernous angiomas, largely because of its relative lack of specificity. Computed tomography findings are compatible with low-grade gliomas, hematomas, granulomas, and inflammatory conditions such as tuberculomas and sarcoidomas. When calcified and located near the dura, cavernous angiomas can even

resemble meningiomas. Computed tomography images also cause small lesions to be missed altogether, and cavernomas, when they present as acute intracerebral hematomas, may not be detected by using nonenhanced computed tomography.

The sensitivity of magnetic resonance imaging to flowing blood and blood products of varying ages, as well as the greater contrast resolution of magnetic resonance imagings, greatly increases the specificity of magnetic resonance imaging compared with that of computed tomography. Combining multiple magnetic resonance imaging sequences has largely eliminated misdiagnosis of cavernous angiomas, because they have relatively specific signal characteristics. Magnetic resonance imaging findings of parenchymal cavernous angiomas demonstrate typical, popcorn like, smoothly circumscribed, well-delineated complex lesions. The core is formed by multiple foci of mixed signal intensities, which represents hemorrhage in various stages of evolution.

Acute hematoma containing deoxyhemoglobin is iso-intense on T1-weighted images and markedly hypointense on T2-weighted images. Subacute hematoma, which contains extracellular methemoglobin, displays hyper-intensity on both T1- and T2-weighted images because of the paramagnetic effect of the methemoglobin.

The interspersed fibrous-containing elements demonstrate mild hypointensity on both T1- and T2-weighted images because they contain a combination of calcification and hemosiderin. The heterogeneous core typically is surrounded completely by a low-signal-intensity hemosiderin rim on T1-weighted images. The hypointensity of this rim becomes more prominent, or blooms, on T2-weighted and gradient-refocused images because of the magnetic susceptibility effects.

Smaller cavernomas may appear as focal hypointense nodules with both T1- and T2-weighted sequences. The small lesions are depicted more clearly and are more numerous on gradient-echo images because of the increased susceptibility effects of the sequences. Sequential gradient-echo images also have been shown to define these punctate lesions further when the echo time is lengthened; this finding suggests that such lesions contain paramagnetic substances.

The magnetic resonance imaging appearance of Cavernous malformations is divided into Types I through IV.[75] The Type II lesion corresponds to the reticulated core of mixed signal intensity with a surrounding hemosiderinring. The Type I lesion generally appears hyperintense on all signal sequences and indicates a subacute hemorrhage. Type III lesions appear iso- to hypointense on most signal sequences, probably indicating chronic hemorrhage. Type IV

lesions are poorly visualized, except on gradient-echo images. On these images, the lesions appear as punctate areas of hypointensity that are similar in appearance to capillary telangiectasias; however, capillary telangiectasias exhibit contrast enhancement and Type IV Cavernous malformations generally do not.[76]

Table 3 Classification of cavernous malformations

Type of cavernous malformations	Appearance on magnetic resonance Imaging
I	Hyperintense on T_1- & T_2-weighted images, subacute hemorrhage
II	Mixed signal intensity on T_1- & T_2-weighted images w/a hemosiderin ring; degrading hemorrhage of various ages
III	Hypo-to isointense on T_1- & T_2-weighted images, chronic hemorrhage
IV	Poorly visualized, except on gradient-echo sequences

When imaged with time-of-flight techniques, the methemoglobin in the central core of a cavernous malformation may mimic flowing blood. However, a subsequent phase-contrast magnetic resonance angiogram obtained with low-velocity encoding (10-20 cm/s) should not

demonstrate flow or abnormal vascularity; this finding helps exclude a vascular lesion.

Typically, cavernous angiomas are not associated with mass effect or edema and do not demonstrate a feeding artery or draining vein, except when associated with other vascular malformations with similar features. Cavernous angiomas are reported to be associated with venous malformations, which typically demonstrate a draining vein.

Most cavernous malformations are angiographically occult, and when they are evident on angiograms, the findings are nonspecific. When the lesions occur in combination with other vascular malformations, as they do in as many as 30% of patients with venous malformations, magnetic resonance imaging characteristics become more complicated and less specific. In these patients, angiography can be helpful in further defining the lesions.

Most cavernous malformations (37-48%) correspond to avascular masses on conventional angiograms. Because of the extremely slow flow of blood through these lesions, cerebral arteriographic findings are often normal. If the lesions are large enough or associated with hematomas, mass effect on adjacent vessels can be appreciated. The avascular appearance is the result of compression or destruction of vascular channels by hemorrhage, thrombosis, and generalized slow flow because of the small size of the

connecting sinusoidal vessels with the peripheral normal parenchymal vessels.

When lesions are smaller and not associated with hematomas, 20-27% of angiograms demonstrate normal findings. Capillary blush is demonstrated at 12-20%. The capillary blush may not be visualized during the first injection; if the injection is repeated a few minutes later with a larger volume and over a longer period, the blush can be demonstrated better. Capillary blush is by no means a specific finding, and it can be seen in a variety of other processes and entities.

Surgical Indications

TABLE-4 Surgical Indications for Brainstem Cavernous Malformations[77]

Exophytic lesions (reaching the pial surface)
Rapid or progressive neurological deterioration
Hemorrhage outside lesion capsule
Significant mass effect
Multiple debilitating hemorrhages

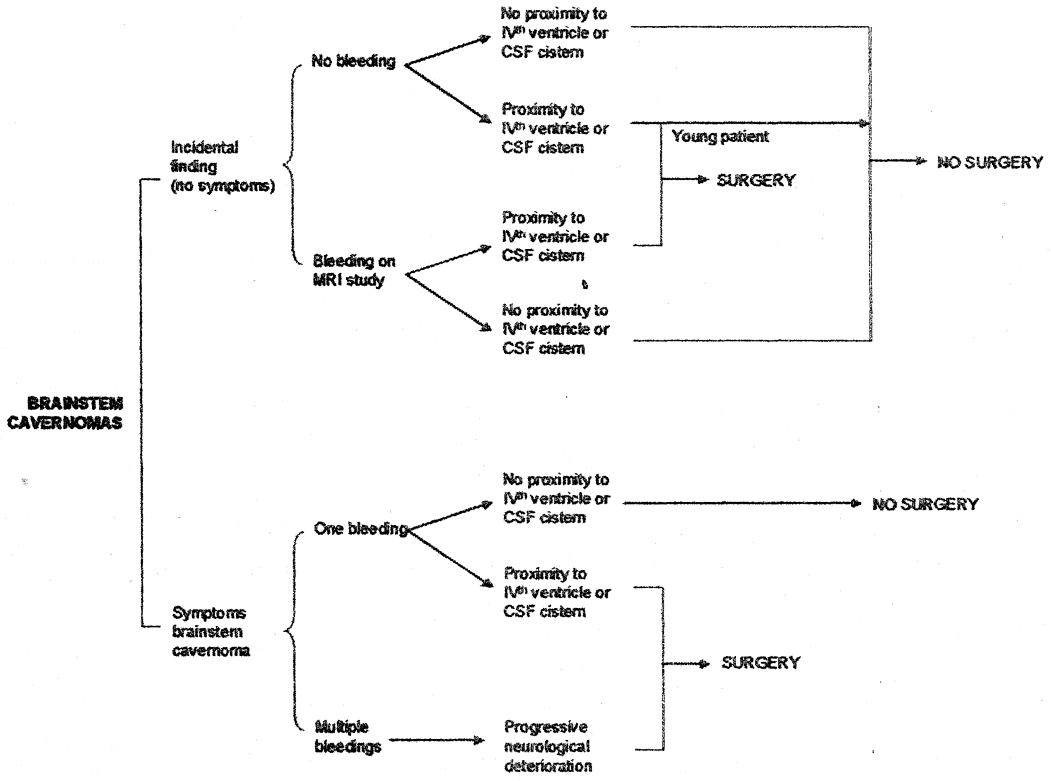
The benefit of surgery on the treatment of brainstem cavernomas has already been reported. Numerous authors have stressed that the complete removal of brainstem cavernous angiomas in patients with recurrent symptomatic hemorrhages is the only choice to avoid further devastating rebleeding-related neurological impairment [1,2,3,11,13,15,55,69,70].

Patients who suffer multiple hemorrhages and in whom the lesion is located close to the wall of the fourth ventricle or lateral cistern should undergo surgery after the last hemorrhagic episode as soon as neurological recovery or stabilization has been achieved. In patients with clinically asymptomatic brainstem cavernomas but with Magnetic Resonance imaging documented bleeding, the indication for surgery will depend on the location of the lesion. Surgery is advised especially in young patients, in whom there is radiological documentation of bleeding and cavernomas bulging into the fourth ventricle. In case of incidental cavernous angiomas found within the brainstem without any contact with the surface in an asymptomatic patient surgery is not recommended preferring instead a conservative approach because of the surgery related risks and possible post operative morbidity. Older (>65 years of age), relatively asymptomatic patients in whom lesions are detected incidentally are normally treated conservatively.

Young patients in whom brainstem cavernomas are found incidentally but in whom previous hemorrhages have occurred, and in whom there is contact between the lesion and the surface of the fourth ventricle or cerebrospinal fluid cistern, may be observed or may undergo surgery depending on the exact location of the lesion and the patient's expectation regarding natural history and the surgery-related outcome after treatment of such lesions. The risk of

spontaneous bleeding and related neurological deterioration, and possible surgery-related complications, should be explained to the patient to help him decide the best treatment.

Occasionally, non operative support of patients with cavernous malformations has been a suggested method of management. However, fatal or worsened outcomes may result if the lesions are not resected. In their meta analysis, Fritschi, et al[55] reported 30 cases that were managed conservatively. At a mean follow-up period of 36 months, 34% of their patients were moderately-to severely disabled or dead. Worse outcomes were documented in 20% of the non surgically treated patients but another four patients (20%) were lost to follow up making a statistical association difficult. Similarly comparison with the surgical group is difficult but the literature supports a course of progressive deterioration in some conservatively managed cases (Table 5).



Flowchart depicting decision making process for surgical intervention

Table 5: Outcome of various series suggesting that surgery has reasonably good outcome compared to conservative treatment.

	Surgery		VS Conservative	
	Fair	Poor	Fair	Poor
Porter	87%	14%	58%	50%
Sami	84%	16%	-	-
Mathiesen	80%	-	39%	60%
Chung	72.3%	27.7%	—	—
Present	60%	40%	40%	—

Patients should not be considered for surgical therapy if they have severe concomitant medical problems or if they have had a single hemorrhagic episode from a lesion that does not reach the pial surface. These patients can be followed conservatively until they suffer at least one more hemorrhage. This rule is especially true if even the thinnest rim of tissue in the floor of the fourth ventricle must be traversed. If patients develop fixed deficits after another hemorrhage, surgery should be offered as a treatment option. Conservative therapy, however, is still a reasonable option if the symptoms resolve completely. Such lesions usually rehemorrhage, especially in young patients, and then often reach the pial surface. Once patients have experienced several hemorrhages, they may be more willing to accept the inherent risks associated with brainstem surgery.

Unlike most other, surgical and medical diseases, children do not always endure surgery on brainstem cavernous malformations better than adults. Pediatric lesions are considered for resection only after multiple episodes of hemorrhage.

Optimal timing of surgery is less well defined. But most of the authors [11,13] recommend surgery in the subacute stage with a delay of several days or weeks after the haemorrhage, when the patient is in a stable condition , it also avoids reactive gliosis, which may occur months after extralesional bleeding . Additionally, in the subacute stage

magnetic resonance imaging allows better differentiation between the haematoma and the vascular malformation itself. Knowing the exact location of the cavernous malformation within the bleeding cavity is valuable for planning the surgical approach.

Statistical comparison showed the presence of fewer motor deficits in the group of patients in whom resection was performed within 3 months post hemorrhage. To facilitate the removal of acute hemorrhage, one should typically wait 3-5 days for a hematoma to liquefy. If the patient is deteriorating rapidly, however, the brainstem may need to be decompressed in an emergent fashion. Acute hematomas tend to be tenacious and to require more manipulation of the surrounding parenchyma than do more subacute, yet liquefied, clots.

Operative Procedure

The goals of surgery are to minimize the amount of normal brainstem tissue traversed while completely excising the lesion and to preserve an associated venous anomaly or malformation .

To determine the best surgical approach `two –point method' can be used in which one point is placed in the center of the lesion and a second is placed where the lesion most closely reaches the pial surface .The two points are connected , and the resultant straight line through the least eloquent tissue dictates the most

appropriate surgical approach .Preoperative permanent neurological deficits , such as seventh or eighth cranial nerve palsies can also influence the choice of approach .Such deficits may make a translabyrinthine or transcochlear approach more attractive.

Intraoperative magnetic resonance imaging with frameless stereotactic guidance and neuronavigation are an invaluable tools and helps to track the surgeon`s focal point with respect to the lesions`s location and operative trajectory.

If a lesion is to be approached through the floor of the fourth ventricle, the location of cranial nerve nuclei becomes relevant .In 1993, Kyoshima and coauthors[78] described "safe entry zones" above and below the facial colliculus .Bogucki and collegues[79] later modified the zones to access intrapontine lesions. The infrafacial zone has a line 2 mm lateral to the median sulcus on its medial border, the hypoglossal triangle on its inferior border, the facial colliculus on its superior border and the vestibular area laterally .The suprafacial zone has the following boundaries: laterally, the superior cerebellar peduncle; medially, a vertical line 2mm lateral to the median sulcus; superiorly, the frenulum veli ; and inferiorly the facial colliculus. Lesions can distort normal anatomy, obscuring these landmarks. In such cases, the facial colliculus can be stimulated directly while the facial nerve is monitored .

Intraoperative monitoring during brain stem surgery is a valuable adjunct to help minimize complications. The ability afforded by neurophysiological techniques to map brainstem cranial nerve nuclei and tracts can provide definitive localization of important structures which may result in reduced morbidity. Katsuta, et al[80] described physiological localization of the facial colliculus by facial EMG monitoring and the use of a stimulating bipolar electrode on the floor of the fourth ventricle to enter the pons and remove a cavernous malformation without damaging the facial nerve.

Strauss, et al,[81] reported on 10 patients with intrinsic brainstem lesions in whom the fourth ventricular floor was mapped for the facial colliculus and hypoglossal trigone to aid in safe brainstem entry. In only two patients did they perform cEMG monitoring. In these two patients the authors noted increasing EMG activity as they approached either the facial colliculus or hypoglossal trigone. In both cases transient cranial nerve morbidity occurred. EMG monitoring of muscles innervated by cranial nerves six and seven provided the following cliniconeurophysiological correlation: 1) lateral rectus EMG activity did not correlate with postoperative abducens palsy; 2) the absence of lateral rectus EMG activity did not assure normal postoperative abducens function; 3) facial muscle EMG activity was sensitive to facial nerve injury; 4) the absence of facial muscle EMG activity was rarely associated with facial nerve

injury; and 5) facial paresis was most strongly predicted by lateral rectus EMG activity.

BAERs are central signals as they relate to the cochlear nucleus and can be monitored during surgery on an intrinsic pontine lesion. BAERs , however reflect only the auditory pathways ; they do not reflect global brainstem function .Thus ,damage to motor or other cranial nerve nuclei can go undetected .

Surgical approaches

When the lesion involves or points toward the floor of the fourth ventricle, a standard suboccipital approach through the vermis suffices. Lesions presenting in the cerebellopontine angle or the lateral pons may be safely approached through a standard retromastoid craniectomy. A more direct (perpendicular) access can be obtained by a standard subtemporal-transtentorial approach when the lesion is high and lateral, by a combined subtemporal-suboccipital approach when the lesion extends more inferiorly, and by a combined subtemporal-presigmoid approach for the more anteriorly located lesions. Anterior or anterolateral lesions of the highest aspect of the pons or of the mesencephalon can be readily accessed by the pterional-anterior temporal approach or by a standard subtemporal approach. Dorsal mesencephalic lesions require a supracerebellar/infratentorial approach or, when they extend more inferiorly, an occipital transtentorial

Some authors have reported that the annual risk of bleeding may be reduced with radiosurgery [48,83,84,85]. On the other hand, other authors [24,85] have reported a higher incidence of radiation-induced complications in the delicate region of the brainstem.[86] Liu KD etal in 2005 analyzed 125 patients with symptomatic cavernous haemangiomas who were treated with GKS between 1993 and 2002 and found that rebleeding rate dropped from 29.2% before treatment to 5% after treatment.[87] Kim MS et al in 2005 studied the benefits of radiosurgery for cavernomas, Sixty-five cavernous hemangiomas were treated with gamma knife surgery (GKS) between October 1994 and December 2002. The lesions were located in the frontal lobe in 12 cases, deep in the parietal lobe in five, in the basal ganglia in five, in the temporal in three, in the cerebellum in three, in the pons/midbrain in six, and in multiple locations in eight cases. The presenting symptoms were seizure in 12, hemorrhage in 11, and other in 19. The maximum dose was 26.78 Gy, and the mean margin dose was 14.55 Gy. The tumor decreased in size in 29 cases, was unchanged in 12, and increased in size in one. In the seizure group, seizures were controlled without anticonvulsant medication in nine cases (81.8%) after 31.3 months (range 12-80 months). Authors favoured GKS as an effective treatment modality for cavernous hemangiomas, especially for those located within the brainstem, basal ganglia, or deep portions of the brain. It can

reduce seizure frequency significantly although this takes time.[88]

In a study reported by Liu AL et al in 2005, 92 patients with 114 Cavernous malformations were treated by GKS between 1994 to 2001and then followed up for 2-8 years (mean 4.1+/-1.9) and analyzed for the magnetic resonance imaging features of Cavernous malformations bleeding, efficacy of GKS, and the complications of treatment.Results showed that among 43 patients who were treated by GKS to control their epilepsy, epileptic paroxysm was alleviated in 36 patients (83.7%), including 12 (27.9%) seizure-free. Rebleeding was confirmed in 9 patients (9.8%) by neuroimage, one of whom died. Transient symptomatic radiation edema occurred in 7 cases (7.6%) within 6-12 months after radio surgery, and one patient underwent open surgery for cerebral decompression. The main pathological changes of cavernoma were coagulation necrosis and the vessels obliterated gradually after radiosurgery. It showed that it is feasible to treat small and surgically high risk Cavernous malformations by radiosurgery and GKS is safe and effective to control the epilepsy caused by Cavernous malformations, and also to bring down the rebleeding rate after a latency interval of several years.

Kim DG et al in 2002 published retrospective clinical analysis of 22 cases of Cavernous malformations treated by radiosurgery. Twenty-two patients with symptomatic

Cavernous malformations were treated by linear accelerator (LINAC) radiosurgery or Gamma knife (GK) between 1995 and 1998[89]. Twenty patients reported at least one episode of bleeding and four had undergone microsurgery before radiosurgery. The remaining two patients presented with seizure without evidence of recent haemorrhage. In 16 cases, the Cavernous malformations were deep-seated, and the others were located in the cerebral hemispheres; four were located at an eloquent area. The volume of the lesion ranged from 0.09 cc to 4.8 cc (mean 1.42 cc) and the mean marginal dose was 16.1 Gy (8-24). The median follow-up period after radiosurgery was 38.3 months. Results showed that there was one case of haemorrhage during the follow-up period and the seizure was well controlled with anticonvulsants. In the group with prior haemorrhage, the bleeding rate of cavernous malformation after radiosurgery (1.55%/year) was lower than that of pre-radiosurgical period (35.5%/year). Six patients showed neurological deterioration following radiosurgery. On the magnetic resonance images at follow-up, the lesion was decreased in eleven patients, increased in one, and no change was found in 10 cases. Thus it showed that radiosurgery may be a good alternative option for treatment of surgically high risk Cavernous malformations

Pollock BE et al in 2000 reviewed their experience at the Mayo Clinic during the past 10 years and evaluated the

efficacy and safety of cavernous malformation radiosurgery. Seventeen patients underwent radiosurgery for high-surgical-risk Cavernous malformations in the thalamus/basal ganglia (four patients), brainstem (12 patients), and corpus callosum (one patient). All patients had experienced at least two documented hemorrhages before undergoing radiosurgery. They found some reduction in the bleeding rate occurs after a latency interval of several years. The risk of radiation-related complications after radiosurgery to treat Cavernous malformations is greater than that found after radiosurgery in AVMs. Regis J et al in 2000 analysed the potential alternative role of radiosurgery and evaluated its safety and efficacy for treatment of drug-resistant epilepsy associated with cavernous malformations by conducting a retrospective multicenter study and found that Gamma Knife surgery can be proposed for the treatment of epilepsy when the cavernous malformation is located in a highly functional area and mediotemporal site was associated with a higher risk of failure[90].

But stereotactic radiosurgery has been associated with high rates of focal neurological deficits , and according to some studies there is no convincing evidence that it substantially reduces the hemorrhage rates [24, 85, 91-94]. Kondziolka and colleagues[48] treated 47 patients with stereotactic radiosurgery and compared pre and post treatment hemorrhage rates. Their patients were not typical

of most surgical series, as there was a preponderance of brainstem or deep seated lesions. They demonstrated a significant decrease in the hemorrhage rate to 8.8% in the first 2 years after treatment and a further decrease to 1.1% in the following 4 years. After the procedure, however 26% of patients experienced a neurological exacerbation , which correlated with hyperintense change in T2 weighted signals; deficits were permanent in 4% .Another study confirmed these findings[85] revealing high complication rate and no significant difference between the post treatment hemorrhage rates and reported natural history of hemorrhage from cavernous malformation .

These series confirmed a decrease in hemorrhage rate over time from 2 to 4 years after treatment .But this reduced hemorrhage rate is not comparable to the zero rebleed rate after complete lesion excision,These results and high complication rates make radiosurgical treatment less favourable for patients with surgically accessible lesions .For patients with deep seated and truly inaccessible lesions, radiosurgery may be considered.[95, 96]

Current radiosurgical protocols advocate reduced treatment dosimetry (not exceeding 15gy at lesion border) in an effort to minimize radiation induced morbidity.[95]

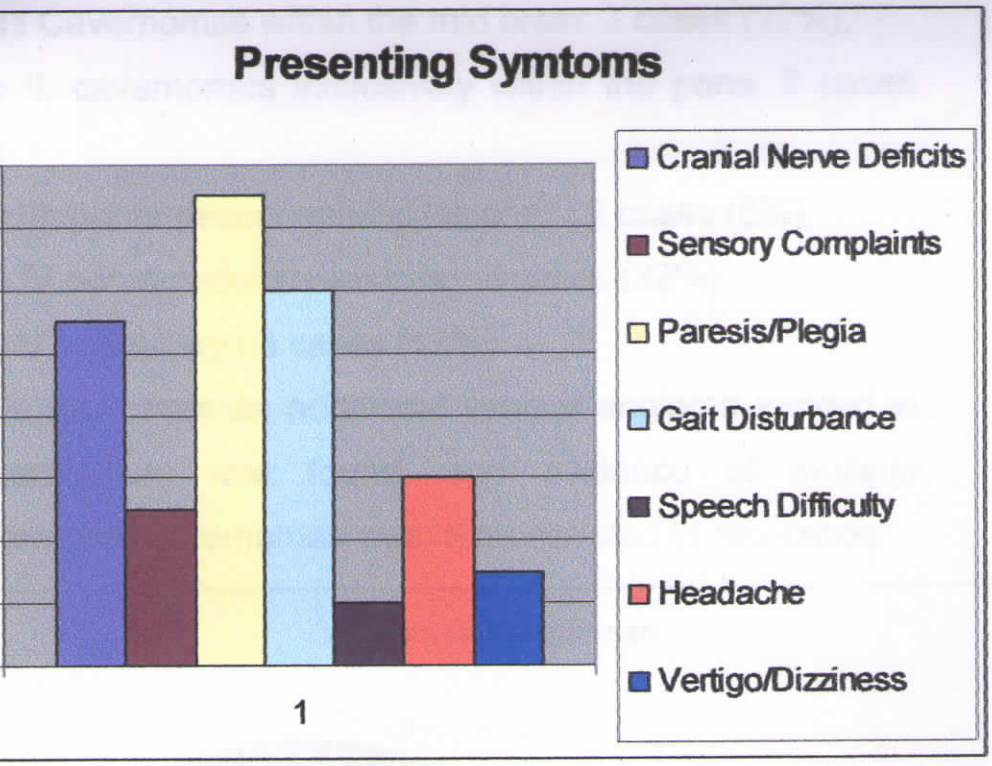
RESULTS AND ANALYSIS

Patient population

There were fourteen males and eleven female patients who ranged in age from 11 to 58 years (mean age 25.4 years). None of the patients had a family history of cavernous malformations. None of the operated patients had evidence of another cavernous malformation in a location other than the brainstem while two patients treated conservatively had associated supratentorial cavernomas.

Presentation

Generally, presentation correlated with lesion location. Most patients presented with multiple neurological signs, which included cranial nerve deficits in 11 patients, sensory complaints (numbness, burning, or paresthesia) in 5, paresis or plegia in 15, ataxia or gait disturbance in 12, speech difficulty in two. Patients also presented with associated symptoms like: headache in 6 patients, vertigo or dizziness in 3. Cranial nerve disturbances, generally sixth cranial nerve and seventh cranial nerve 21 cases [84%]), were the most common neurological deficits, followed by focal motor deficits (15 cases 60%).

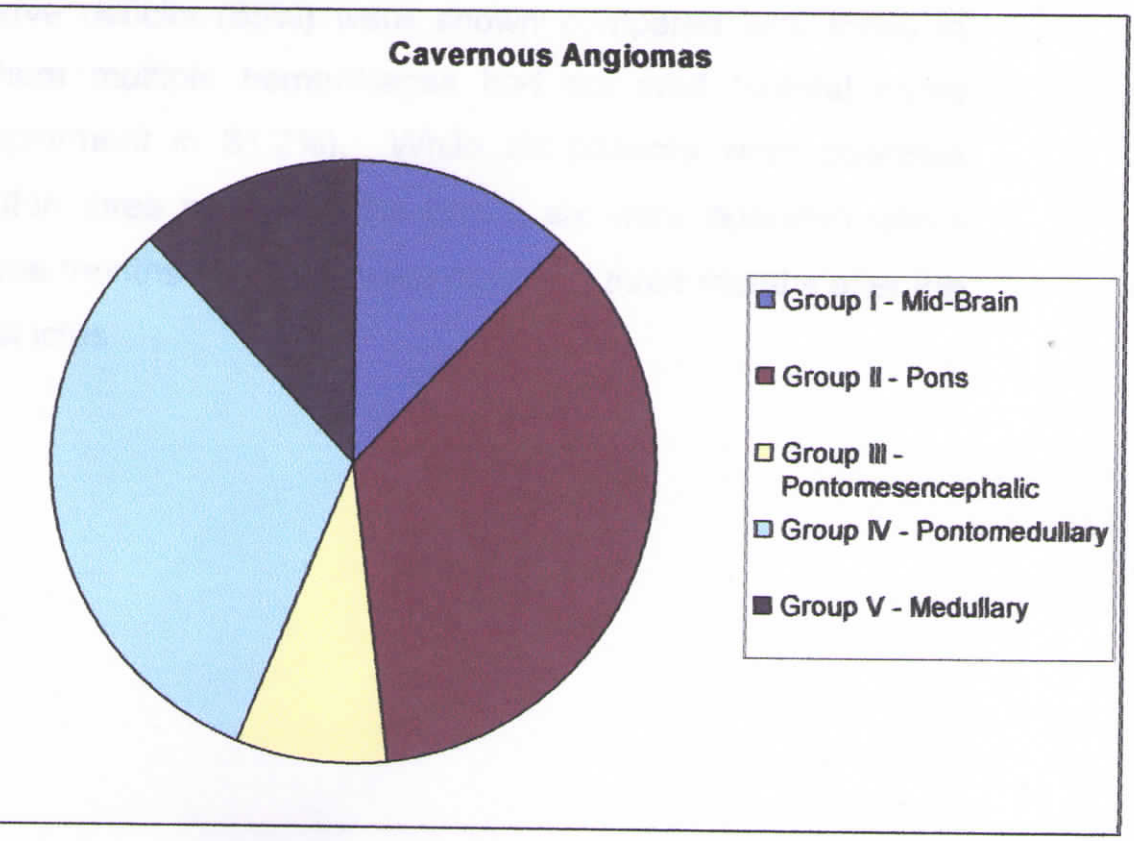


ology

Preoperative Magnetic Resonance imaging studies ately demonstrated the brainstem lesions and signs of ing in all patients. Signs of bleeding were based on the presence of a hyperintense signal on nhanced T1-weighted Magnetic Resonance images ned in the acute phase just after the hemorrhage or the arance of the classic hemosiderin ring visualized around sion on T2-weighted sequences. Based on their axial sions, cavernous angiomas were divided into five s.

roup I Cavernomas within the mid brain: 3 cases (12%),
roup II, cavernomas exclusively within the pons: 9 cases
6%)
roup III, pontomesencephalic lesions: 2 cases (8%),
roup IV pontomedullary lesions: 8 cases (32%)
roup V medullary : 3 cases (12%).

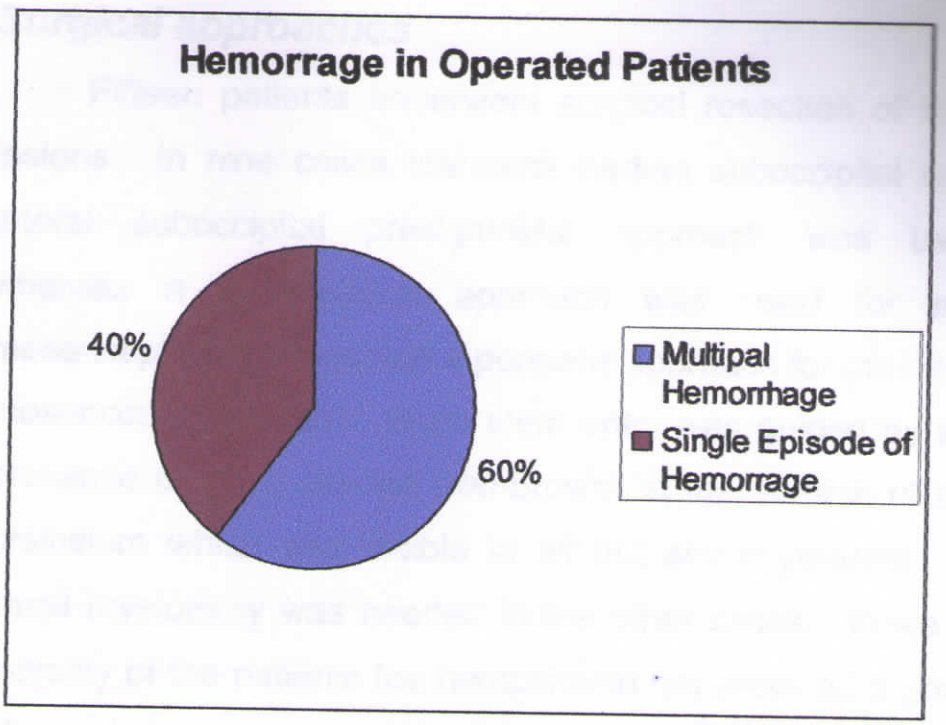
In two cases an additional venous angioma located in e cerebellum was found, and evidence of multiple pratentorial cavernomas was demonstrated in two cases.

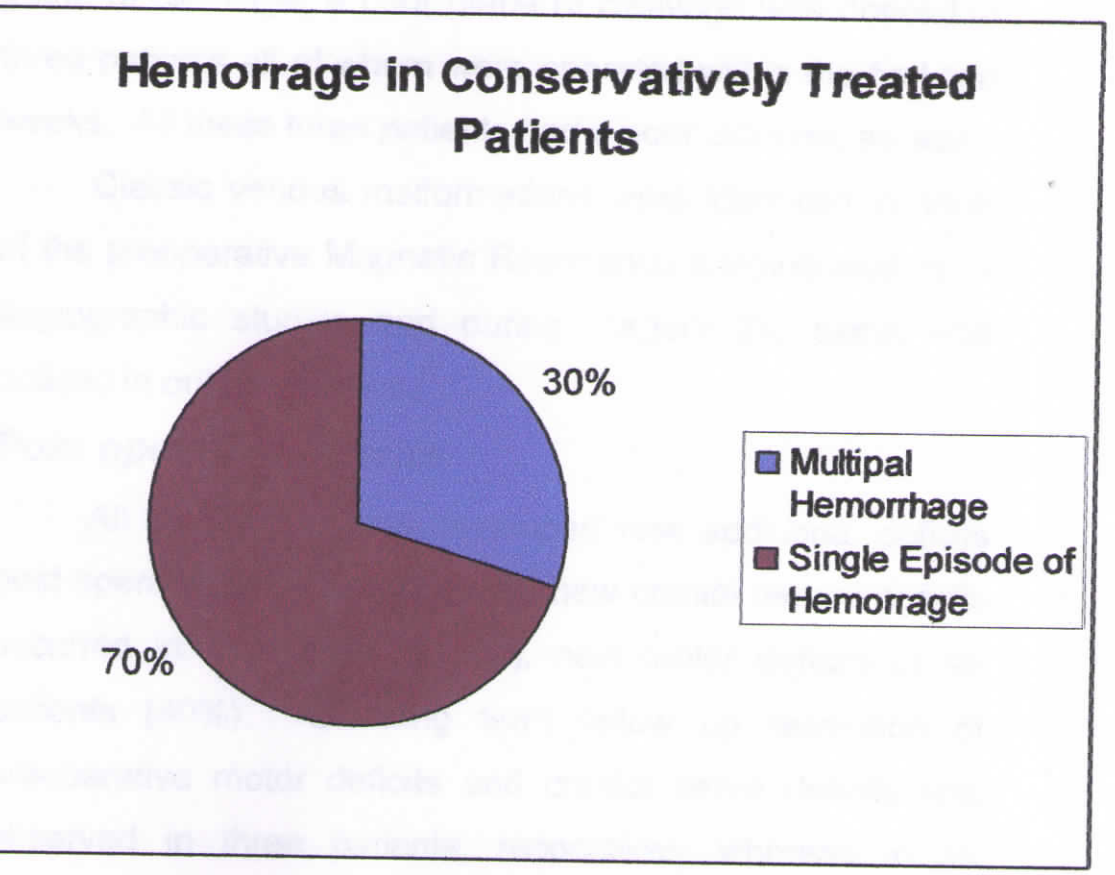


emorrhage from Cavernomas

All twenty five patients presented with at least one inistem hemorrhage at the time of admission. Multiple

hemorrhages were demonstrated in nine and a single episode of hemorrhage had occurred in six of the operated patients. Of the ten patients treated conservatively seven had only a single episode of bleed. Multiple hemorrhages were more frequent in cases of pontomesencephalic cavernous angiomas compared with pontine and medulla oblongata lesions; however, the difference was not statistically significant. In the 6 patients in whom only one episode of cavernous bleeding had occurred, fewer cranial nerve deficits (65%) were shown compared with those in whom multiple hemorrhages had occurred (cranial nerve impairment in 81.2%). While six patients were operated within three weeks of the bleed, six were operated within three months and three were operated three months after the last ictus.


Hemorrage in Operated Patients
40%
60%
Multipal Hemorrhage
Single Episode of Hemorrage


Hemorrage in Conservatively Treated Patients
30%
70%
Multipal Hemorrhage
Single Episode of Hemorrage

Surgical approaches

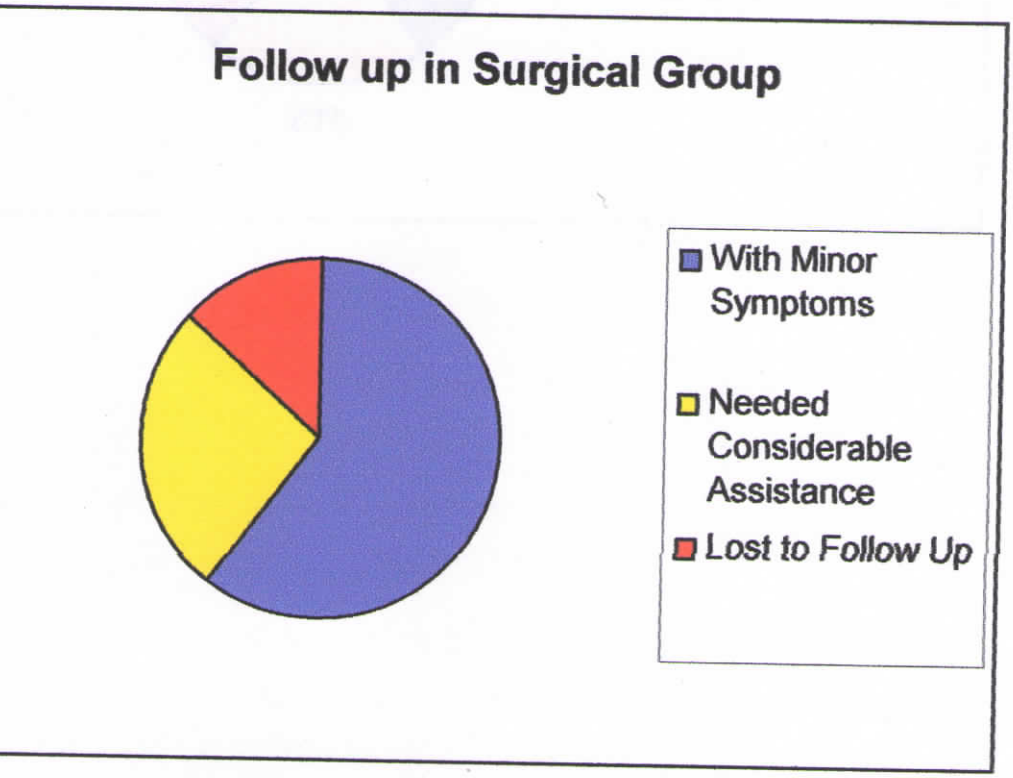
Fifteen patients underwent surgical resection of their lesions. In nine cases standard median suboccipital or a lateral suboccipital presigmoidal approach was used whereas a subtemporal approach was used for two mesencephalic lesions and a poppens approach for the other mesencephalic lesion. Brain stem entry was guided by the presence of color change (red-brown) at the surface of the brainstem which was visible in all but seven patients. A small myelotomy was needed in the other cases. While in majority of the patients the hemosiderin rim provided a good plane of cleavage, a poor plane of cleavage was noticed in three patients all of whom were operated within the first two weeks. All these three patients had a poor outcome as well.

Classic venous malformations were identified in none of the preoperative Magnetic Resonance imaging studies or angiographic studies and during surgery the same was noticed in only two cases.

Post operative deficits

All but two patients developed new additional deficits post operatively. Postoperatively new cranial nerves deficits occurred in 5 patients (33.3%), new motor deficits in six patients (40%). On long term follow up resolution of preoperative motor deficits and cranial nerve deficits was observed in three patients, respectively whereas in six

13 patients were able to engage in Activity of Daily Living with minor symptoms. Four patients did not recover well and needed considerable assistance at the time of the last follow. In the non surgical group, four (40%) of 10 were the same or better, two (20%) of 10 were static, and four non surgically treated patients were lost to follow up. We observed that very early surgery (within two weeks), multiple bleeds, poor plane of cleavage are poor prognostic indicators.



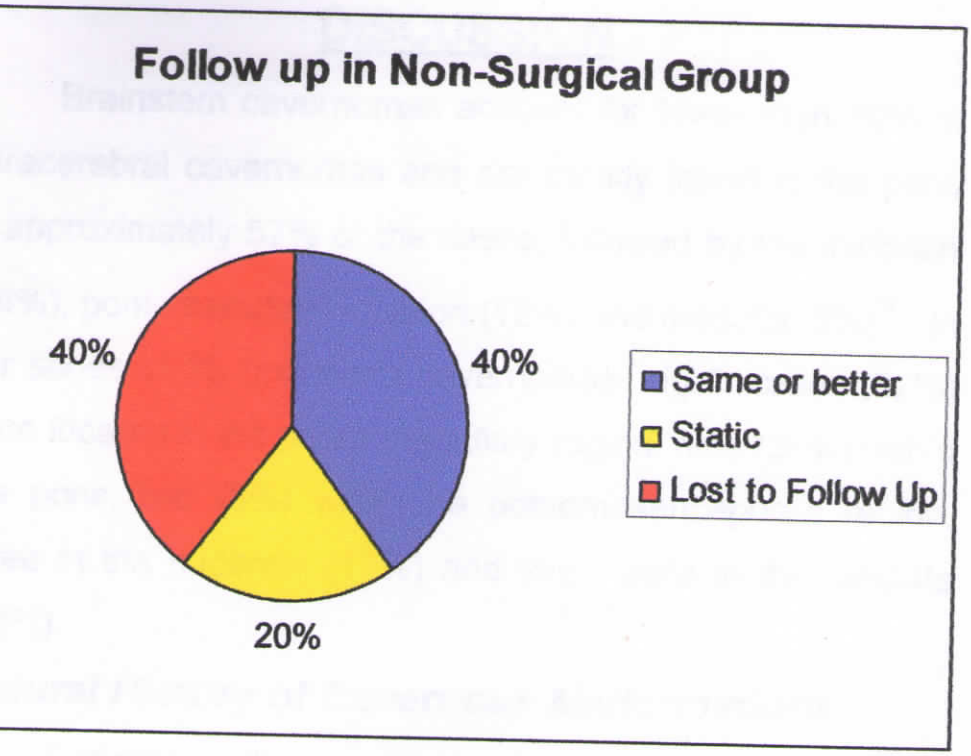
patients, no change in neurological status was observed immediately after surgery. Analysis of immediate postoperative results showed that in patients with pontomesencephalic and pontine cavernous angiomas as well as those in whom multiple preoperative brainstem hemorrhages had occurred, a higher probability of postoperative deficits were seen but their statistical significance is doubtful. In terms of the preoperative time interval between the last hemorrhage and surgery and its relationship to postoperative results, analysis showed that those with postoperative deficits underwent surgery significantly earlier than the others.

Complication and mortality

There were two cases of surgery related death and two patients had a prolonged stormy post operative course with need for tracheostomy. In the early post operative period, three additional patients received tracheostomies, feeding tubes, or both. At long term follow up review, only one patient still had a tracheostomy and feeding tube; the status of two patients was unknown.

Follow up

The mean follow up period was 2.2 yrs. Thirteen patients of the operated fifteen patients were available for long term follow up. Of these six patients remained the same and four developed new cranial nerve deficits. Nine (69%) of


Follow up in Non-Surgical Group
40%
40%
20%
Same or better
Static
Lost to Follow Up

DISCUSSION

Brainstem cavernomas account for fewer than 20% of intracerebral cavernomas and are mostly found in the pons in approximately 57% of the cases, followed by the midbrain (14%), pontomedullary junction (12%) and medulla (5%)[3]. In our series of 25 brainstem cavernomas, eight cases (32%) were located in the ponto medullary region, nine (36%) within the pons, two (8%) within he pontomesencephalic region, three in the midbrain (12%) and three were in the medulla (12%).

Natural History of Cavernous Malformations

Patients with cavernous malformations may be relatively asymptomatic or they may be neurologically devastated. Hemorrhage from brainstem lesions may be more likely to elicit symptoms than hemorrhage from lesions of similar size in other locations (for example, cerebral hemisphere) because of the relatively larger number of the critical tracts and nuclei in this region[2]. The most common presentation in the current series included any combination of cranial nerve deficits, motor or sensory disturbances, headache, ataxia, vertigo, nausea and vomiting. The onset of symptoms can be gradual; however, it usually is abrupt and may manifest as new or as an exacerbation or recurrence of existing or previous neurological deficits. These lesions may also mimic demyelination, infarction,

neoplasm or infection in their clinical presentation[1,3]. Even small hemorrhages from brainstem lesions are likely to elicit neurological symptoms. In our series, all patients presented with hemorrhage and most with multiple hemorrhages. However, the interval between hemorrhages was widely divergent and unpredictable.

Several authors have estimated that the risk of hemorrhage in cases of brainstem cavernomas is approximately 0.7% per year per lesion[1,13]. In the present series, 48% of the patients had suffered more than one episode of bleeding. The hemorrhage rate for brain stem cavernomas is quite high. Porter et al have reported a rate of 5% per person per year.[25] This contention is supported by Porter and associates, who prospectively followed 100 cases of patients with cavernous malformations and found the hemorrhage rate to be 30 times greater for infratentorial lesions compared with supratentorial ones[15]. Patients with infratentorial cavernous malformations who presented with hemorrhage bled again within 26 months[1,3]. In their series of 50 patients with brain stem cavernomas Sathi, et al (unpublished data) reported a 16.9% rehemorrhage rate per lesion per year while Fritschi et al[55] have reported a 21% rebleeding rate. In a prospective report, the annual rate of repeated hemorrhage for brainstem lesions reported by Kondziolka[95], et al, was 5% per lesion per year compared with 2.4% over all. In Porter et al's[25] series the repeated

hemorrhage rate is a as high as 30% probably, probably reflecting a selection bias because many patients were referred after conservative management had failed. Interestingly, multiple hemorrhagic event were more frequent in patients with pontomesencephalic cavernomas (75%), followed by those with pontine (42.9%) and medulla oblongata lesions (25%)[3,69]. In patients in whom multiple brainstem hemorrhages had occurred a greater number of cranial nerve deficits (81.2%) were present compared with those in whom only one hemorrhage event occurred (65%). Further more, complete pre operative neurological recovery after brainstem bleeding was found in 20% of out patients with one episodes of hemorrhage compared with 6.25%) in those with multiple pre operative hemorrhages. Various authors have reported that multiple bleeding episodes increased the likelihood of a persistent deficit because 50% of patients with lesions in the brainstem or thalamus had debilitating and lasting deficits after rehemorrhage[95].

Despite the risk of significant neurological impairment related to the location of such lesions within the brainstem, bleeding is usually limited because of its low flow pattern[11, 70]. Some authors have suggested that intralesional bleeding due to the rupture of caverns within the cavernomas, formation of new cysts, and possible reactive angiogenesis may be responsible for the dynamic nature and growth of

some lesions. On the other hand significant inrtravavernous hemorrhage may also destroy the lesion.

Whether pregnancy increases the risk of hemorrhage in patients with cavernous malformations is unclear. Some authors, however, have suggested that female hormonal factors may play a role[1,3]. Seven (11%) of 52 female patients in Porter series suffered a hemorrhage during pregnancy. They concluded that estrogen may play a role in the propensity to bleed. Estrogen receptors have been observed in a few cavernous malformations obtained in females by some authors.[1, 97, 98]

Surgical Outcomes

Surgical outcome did not conclusively relate to lesion location except in a few possible cases. Surgery is ideally deferred in patients with intrinsic lesions in the paramedian floor of the fourth ventricle unless the patient is rapid deteriorating. Unless the lesion is clearly exophytic, alternative entry points like the anterolateral pons should be considered as there are fewer complications associated with entering the brainstem in this region[100]. Intraoperative electrophysiological monitoring of the floor of the fourth ventricle has been used by different authors to determine safe entry zones to approach the lesions and thus avoid direct damage of cranial nerve nerve nuclei in the brainstem[70, 100]. In our series, the incidence of new post operative neurological deficits was clearly lower than pre

operative deficits caused by one or multiple cavernous angioma hemorrhages within the brainstem. The rate of new facial palsy, for instance, was only 26.1% and that of motor deficits was only 40% compared with pre operative incidences of 53% and 66.6%, respectively. (table.5).

Table 6: New post op deficit vs morbidity due to bleed

	Porter's	Present
Facial palsy		
Following surgery	22.1%	26.1%
Following Bleed	44%	53.3%
Motor deficit		
Following Surgery	8%	40%
Following Bleed	47.2%	66.6%

In a review of the literature, Fritschi, et al[55], reported that 74% of the surgically treated patients had recovered completely or had minimal disability. Recently, Amin-Hanjami and associates[24] reported that 85.7% of their patients were "improved" or stable at last follow – up. These figures are comparable top those reported in the current series in which 60% of the patients were the same or better at last follow-up review.

Morbidity and Mortality Rates

Although an overall morbidity and mortality rate is apparently high (Bertalanffy[11] (33%), Simard, 70%), one must remember that these patients underwent extensive skull-base dissections and that in most patients the

complications were temporary and treatable. More recently however Amin – Hanjami[24] and associates reported a 14.2% persistent disabling complication rate in their series of 14 patients. These figures are comparable to the complication rate of 12% in the current series.

Decision for surgery

In our series of the six patients who had poor outcome four were operated within the first two weeks. Contrary to other reports we found a poor plane of cleavage in two of the three patients operated in the first two weeks and therefore we prefer to defer surgery in the acute and sub acute phase.

CONCLUSION

- The natural history of cavernous malformations of the brain stem is worse than in other CNS locations.
- The hemorrhage rate for cavernomas of the brain stem is higher than rates of cavernous malformations in other locations and brain stem cavernomas that hemorrhage once are more likely to hemorrhage again.
- Surgical resection can be achieved with acceptable results.
- Surgery should be considered for symptomatic brain stem cavernomas that reach the surface and have caused multiple hemorrhages.
- Surgery is ideally deferred in the acute stage and preferably done after three to four weeks.
- Major morbidity seems to be mainly related to preoperative brainstem hemorrhages and less to surgical treatment.
- Cases of asymptomatic patients or patients who have completely recovered from a single hemorrhage, however, may be followed conservatively.
- Venous anomalies, if associated with cavernous malformations of the brainstem, should be preserved.
- The benefit of stereotactic radiosurgery in the treatment of cavernous malformations has yet to be demonstrated.

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PROFORMA

Name :

Address :

1. Hospital No. :

2. Age :

3. Sex :

4. Presentation :

5. Recurrent bleed : 1,2,3……
9=No

6. Family h/o : 1=Yes
2=No
9=Not known

7. Duration :

8. Multiplicity : 1=Yes
2=No

9. Location :

Presentation		
1. Hemiparesis	2. Ataxia	3. Diplopia
4. V-VIII CN palsy	5. Dysphasia	6. Vertigo
7. Hemianesthesia	8. ICP	9. Tremor
10. Alt.sensorium	11.Gaze palsy	12. Fever
13. Parinauds	14.Hiccup	15. Resp.
16. Bradycardia		

Location	
1. Midbrain	2. Brachium conjuctivum
3. Midbrain – pons	4. Pons
5. Brachium Pontis	6. Pons-medulla
7. Medulla	8. cervicomedullary

10. Management : 1=Surgery
2=Conservative

11. Surgical approach : 1=Midline suboccipital 2=Poppens
3=Subtemporal 4=Transylvian

CT/MRI

12. Microh'ages :

13. SAH :

14. IVH :

15. Hemosiderin rim :

16. Size of the lesion : 1=<1cm, 2=1-3cm, 3=>3cm

Surgery

17. Distance from brainstem surface :

18. Plane of cleavage : 1=good 2=poor

19. Complications :

20. Outcome :

1=Deterioration in power
2=Tracheostomy & ventilation
3=Infection
4=Rec.h'age
5=Gaze palsy
6=Fresh cranial nerve deficits
7=Reexploration