SREE CHITHRA THIRUNAL INSTITUTE FOR
MEDICAL SCIENCES & TECHNOLOGY

HAEMANGIOBLASTOMA OF THE NEURAXIS - A RETROSPETIVE STUDY

RAVI GOPAL VARMA

CERTIFICATE

I, Dr. RAVI GOPAL VARMA .....hereby declare that I have actually performed all the procedures listed/carried out the project under report.

Signature.....

Place : **Trivandrum**

Date : 9.11.98

Name in capital letters

RAVI GOPAL VARMA

Forwarded. He has carried out the ~~two~~ project**s** under report

Signature
Head of the Department

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	Page	of
	Date	

LIST OF PROCEDURES DONE

PROJECT REPORT

TITLE OF PROJECT : **HAEMANGIOBLASTOMA OF THE NEURAXIS - A RETROSPECTIVE STUDY**

NAME : **DR. RAVI GOPAL VARMA**

PROGRAMME : **M.Ch NEURO SURGERY**

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Name	
Page	of
Date	

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CONTENTS

INTRODUCTION

Hemangioblastomas are benign vascular neoplasms occuring as a single lesion, multicentric, as a sporadic or familiar disease complex. It often constitues the retinal and neuraxial component of Von Hippel Lindau Phakomatosis. It is an autosomal dominant inheritant disease complex. Certain chromosomal abnormalities have also been associated with haemangioblastomas. Ninety two percent of these tumors are infratentorial in location and are amenable for surgical excision. Surgery forms the only effective modality of treatment and total excision entitles a cure.

A retrospecitive analysis of forty one operated cases of CNS haemangioblastomas over a 20 year period was done to elucidate the presenting symptoms, surgical procedure, complications, recurrence and outcome.

AIMS & OBJECTIVES

A retrospective 41 analyses of operated cases of CNS haemangioblastoma over 20 year period was done with the following aims and objectives.

1. To elucidate the incidence and prevalence of CNS haemangioblastoma and VHL syndrome.
2. To analyes the distribution and clinical profile of these lesions.
3. To assess the outcome with respect to available treatment modalities.
4. To determine the overall prognosis as compared to other CNS tumors.

MATERIALS AND METHODS

Fortyone cases of CNS haemangioblastomas treated over a period of 20 years from 1977 to 1997 at SCTIMST, were retrospectively reviewed. All the available data regarding clinical presentation, radiological investigations opthalmological finding, surgical technique performed and outcome were analysed. All patients who underwent surgery had histological diagnossis which was confirmed by the neuropathologist. The modes of presentation and their duration, the various locations and the surgery performed were analysed. The surgical procedure consisted of cerebrospinal fluid diversion procedure, when the patient had significant hydrocephalus. Based on C.T. Scan finding the lesions were classified into 3 types. Type I cystic Type II cystic with solid component, type III solid. The outcome at discharge and subsequent followup were classified as:-

Grade I - Normal

Grade II - ADL (Activities of daily living) without support.

Grade III - ADL with support.

Grade IV - Vegetative state.

Grade V - Dead

Most patients at follow up were assessed with C.T.Scan to locate any recurrence, extent of tumour excision and state of hydrocephalus. The type of lesion on C.T.Scan and surgical outcome and recurrence were correlated and observations derived. The results of these analysis are discussed subsequently.

REVIEW OF LITERATURE

Definition

The word haemangioblastoma was coined by Cushing and Bailey in 1928. Haemangioblatastoma are true neoplasms made up of vascular and intervascular (stromal) cell proliferation included in a reticular network[1].

Haemangioblastomas as an entity, have its own anatomical, pathological, clinical and epidemiological characteristics that clearly seperate them from other vascular tumors of the neuraxis. They are :-

1. Preferential location in the cerebellum though they may grow anywhere in the neuraxis.
2. High frequency of simultaneous or subsequent multiple tumors.
3. Possible production and release of an erythropoetic factor leading to secondary erythrocytosis.
4. Potential association with retinal haemangioblastoma (Von Hippel tumor) and or lesions situated within the CNS (Lindaus tumor) and forming VHL complex or disease.
5. Presence of inherited form.

The term haemangioblastoma stands for a single lesion, where as haemangioblastomatosis is for multifocal CNS lesion.

VHL complex minimal criteria are[2]

1. More than one hemangioblastoma within the neuraxis (strongly implying multicentricity).

2. A solitary haemangioblastoma in the neuraxis associated with at least one visceral manifestation.
3. Any clinical manifestation of VHL syndrome in a first degree relative of an individual known to have VHL syndrome.

More than 30 manifestation of VHL syndrome have been described. They are :-

Table I - Associated lesions in Von Hippel Lindau Complex

- Pancreatic cysts
- Pancreatic adenomas
- Islet cell carcinoma of pancreas
- Adenocarcinoma of pancreas
- Liver cyst,angioma,adenoma
- Renal cyst,angioma,adenoma
- Renal cell cacrinoma
- Splenic cyst,angioma
- Lung cyst,angioma
- Omental cyst
- Adrenal angioma,adenoma
- Pheochromocytoma
- Epididimal cyst,adenoma
- Ovarian cyst,carcinoma

Historical Perspective

The first description suggestive of a haemangioblastoma was by Hughlings Jackson in 1872 in his article in Medical times and Gazette. Here he describes a 20 year old female with a cerebellar lesion, whose sister had died of seizures. Panas and Remy were the first to describe a retinal

haemangioblastoma in 1879 and was termed "cystic detachment of the retina". The first description of both CNS and visceral lesion was reported by Pye-Smith in a 27 year old male at autopsy in 1885 who had cerebellar cystic lesion with several renal and pancreatic cysts. The first contribution of Eugen Von Hippel a German ophthalmologist was a vivid description of the fundoscopic appearance in a 23 year old man which showed a rounded mass located at the periphery of the retina in 1895 and reported that it was a cystic capillary angiomatosis of congenital origin.In 1913 Koch reported autopsy findings of a 47 year old male affected by cystic lymphangiomas of pancreas and liver and renal cysts with angiomatosis tumor of the cerebellum and spinal cord (probably the first description of an intra medullary lesion). In 1922 Berblinger published autopsy findings in a 27 year old female with haemangioblastomas of the medulla oblongata, a right retinal angioma and pancreatic and renal cysts. In the same year many others described lesion in the medulla with associated syrinx and visceral manifestations.

In 1926 Arvid Lindau a Swedish pathologist in Lund, published his famous dissertation entitled "Studies uberklein Hirnzysten,Bau,Pathogenese Und Beziehungen Zur Angiomatosis Retinae"[3]. In this he reported 16 cases of cerebellar cysts with vascular mural nodules. He compared these lesions with other cystic lesion of the crebellum and also described its association with other cystic lesion of the cerebellum. He also described its association with other lesions. He pointed out the possible familial inheritance and its rate, and characterised the disorder which he termed"Angiomatosis of the central nervious system". He suggested misdevelopment during the III

month of foetal life and stated that the disorder which appeared as a mesodermal dysplasia had some analogy with tuberous sclerosis and Von Recklinghausen neurofibromatosis of ectodermal origin.

With due respects to all involved in the description and definition of this disease, most importance and most credit should be given to Harvey Cushing who on September 14, 1908 successfully operated on a 28 year old man to remove a large solid microcystic tumor of the right cerebellar haemisphere (5x4cm). Twenty years later when he wrote his monograph Cushing examined his patient who was healthy[4] and well, whose HPE was haemangioblastoma of cellular type. It is worth noting that this successful operation was performed 3 years prior to advent of vascular clips and 18 years before Bovie introduced electrocoagulation in neurosurgery.

Incidence

Haemangioblastoma are relativity uncommon tumours. Two prominent series are listed in table II. Infratentorial haemangioblastoma account for less than 2% of all intracranial tumors[4,63].

Table II

Series	Haemangioblastoma	CNS tumours
Poinier et al (1983)	36	2000
Winkelman (1978)	66	2356
Total	102	4356

LOCATION

I. Posterior Cranial Fossa Haemangioblastoma (Infratentorial)

The most common location of hemangioblastoma is the posterior fossa. They constitute about 92.6% i.e., pooling of 8 series, 464 out of 500 cases reported.

Table III

Series	Haemangioblastomas	
	Infratentorial	All CNS
Bock & Brenner (1970	39	42
Jeffreys (1975)	67	76
Mondkar et al (1967)	112	119
Palmer (1972)	80	81
Papo et al (1961)	44	45
Robinson (1965)	23	24
Neiber et al (1969)	58	61
Leu and Ruttner (1973)	41	52
Total	464	500

Almost 95% of posterior fossa haemangioblastoma are located in the cerebellum. Pooling of 8 series gave total 534 cerebellar tumors among 566 tentorial hemangioblastoma.

Table IV

Series	Cerebellar Haeman-giobl	Brain stem Haefman-giobl	Total
Bock and Brenner (1970)	38	1	39
Borck & Tonnis (1955)	43	3	46
Krayen Buhl & Yasargil (1958)	41	4	4
Leu & Ruttner (1973)	41	0	41
Muller - Jansen (1984)	40	4	44
Olivecrona (1952)	65	5	70
Round Table of the SFNC (1985)	230	6	42
Singonas (1978)	36	6	42

a. Cerebellar Haemangioastoma

In the cerebellum,haemangioblastomas may be located in the hemispheres,less frequently in the vermis and rarely in the tonsils.

In a series of 224 cerebellar haemeangioblastoma topographical distribution was as follows[5]:

Table V

Hemispheres	177 cases, i.e. 79%	(R-78, L-99)
Vermis	38 cases, i.e. 17%	(Ant sup & Middle - 23)
Tonsil	9 cases 44%	(Post inf - 15)

Cerebellar haemangioblastomas may exhibit 4 macroscopic aspects:

Type I - Simple Cyst

Type II - Large cyst with mural nodule

Type III - Solid tumor

Type IV - Solid tumor with internal small cysts

Therefore there are two predominantly cystic variants and two predominantly solid variants.

Type I - Has feature of a simple cyst containing xanthochromic fluid, with a smooth wall on which a few very thin vessels are seen but no obvious mural nodules is seen. On detailed careful and minute microscopical examination of the cyst wall the mural nodule may be seen. They constitute about 4% in literature.

Type II - Macrocystic haemangioblastoma is the most common variant and constitute 60.6%. It appears as a spheroid a or ovoid cyst often large (30-50mm dia meter), filled with xanthochromic fluid.The mural nodule is reddish orange & lies on the pial surface and its size is often smaller than that of the cyst (5.15mm dia meter). The wall of the tumoral cyst is constituted by cerebellar tissue flattened by the transudation of fluid originating from the nodule. The nodule is the only cause of formation of the cyst which has no true capsule[4].

Type III - They are solid haemangioblastomas and is less frequent (26.2%). It appears as a dense spheroid red colored tumour (size 30-40mm in dia meter). It has no true capsule and has rich blood supply.

Type IV - Solid hemangioblastomas with internal small cyst. They constitute 9.1%. It is similiar to the solid variety but with multiple small cyst with in the solid part (5mm in dia meter).

b. Brain Stem Haemangioblastomas

Haemangioblastomas can occur in any part of the brain stain. The commonest sites are caudal part of floor of IV ventricle (area postrema), the dorsolateral aspect of medulla and the cervicomedullary junction.

Distribution according to collection from literature are 62 in number. The topographical distribution is as follows[5]:

Pons	-	2
Dorsal medulla	-	17
Floor of IV ventricle	-	16
Cervicomedullay junction	-	17
Extensive	-	10

c. Cerebellopontine Angle (CPA) Haemangioblastoma

It very rarely seen in the CPA. This location represents from 0.8 to 3.3% of all haemangioblastoma of the posterior fossa[5]. In such a location almost the whole tumor exhibits itself as a subpial extraparenchymal lesion.

II. Spinal Haemangioblastoma

Spinal haemangioblatastomas accounts for 5% all spinal tumors. Pooling values reported in 8 series gives an average of 5% (59 out of 1156).

Table VI - Haemangioblastoma vs other spinal tumours

Series	Haemangio-blastoma	Other
Christionens (1965)	1	30
Fornari et al (1988)		
Guidetti & Fortuna (1987)	6	74
Murota and Symon (1989)	18	310
Sloof et al (1964)	10	301
Solomon and Stein (1988)	8	60
Winkelmann (1978)	4	278
Yasui et al (1988)	7	22
Total	59	1156

Intradural spinal haemangioblatastoma may be classified into Intramedullary, Subpial, Extramedullary of spinal roots[6]. Intramedullary lesion are commonly situated between C_3 & D_1 and D_7 & L_1 (at the cervical and lumbar enlargements). Spinal root haemangioblastoma occurs at the junction between the root and cord and are commonly seen with the posterior roots. It may involve roots of the cauda equina. Hour glass spinal root haemangioblastomas have also been described[6,7].

Extradural spinal haemangioblastomas are extremely rare. Two cases have been reported in literature of extradural spinal haemangioblastomas of the vertebral bodies[8] one of them in association with cerebellar and retinal

hemangioblastoma and bilateral renal cell carcinoma in addition to a positive family history.

Macroscopically they may be either solid or cystic[9,10,11]. The association of intramedullary spinal cord tumor with one or more intraspinal cysts have been well documented [6,9,10,11,12,13.14,15,16,17].

These cysts contain high protein fluid. They may not be in juxtaposition with the haemangioblastoma. They may be multiple or extensive into the spinal cord in the presence of a single intramedullary tumor. Several theories have been proposed to explain the origin of these cysts.

1. Similar to tumor cyst as seen in the cerebellum are due to transudation of fluid from tumor[3].
2. As hydromyelia secondary to circulatory disturbance and ischemia or tumoral haemorrhage into grey matter followed by glosis[18].
3. A true syringomyelia of congenital dysraphic origin[17].

III. SUPRATENTORIAL HAEMANGIOBLASTOMA

Hemangioblastomas occuring supratentorial have histological pattern very similar to other cerebral vascular tumor especially angio blastic meningioma and therefore was a subject of great controversy and debate. Baily,Cushing and Eisenhard[19] gave the term angioblastic meningioma to describe a tumor that has great resemblance to the histological description of haemangioblastoma but of extraaxial origin. Light microscopic[20] and electron microscopic analysis[21] does not allow any differentiation. They are

Spontaneous progression is the rule; four stages have been defined[45].

First stage : progressive vascular enlargement and tumor growth.

Second stage : Onset of hemorrhages and exudates.

Third stage : Massive exudates and retinal detachment.

Late stage : Secondary glaucoma and destruction of eye.

Spontaneous evolution ends in visual loss. According to literature retinal involvement appears more frequently unilaterally with an incidence of slightly less than 2/3rd of all cases [5].

b. Intraorbital or optic nerve haemangioblastoma

A few cases of haemangioblastomas involving the intraorbital part of the optic nerve have been reported by Hotta H. et al.[46] and S.Miyugi J.et.al[47].

PATHOLOGY

1. Light microscopy

Haemangioblastoma constitute of a double tissue proliferation. They are vascular and intervascular cells. The characteristic pattern is of vascular channels made up of capillaries of normal structure and intervascular spaces occupied by trabeculae of rounded or polygonal cells,with central spheroidal nucleus and a slightly stained,partly foamy cytoplasm-stromal cells. According to Cushing and Bailey the relative extent of capillaries and intervascular tissue leads to the recognition of three histological variants[4].

Reticular or capillary - Commonest type composed largely of a fine mesh of blood spaces and channels of capillary structure. In this type intervascular tissue hardly develops.

Cavernous variant - In addition to the above features there are grossly enlarged vascular channels and capillaries are dilated into large sinuses.

Cellular variant : Here the intervascular tissue is most well developed and is predominantly composed of compact lobules of pale eosinophilic stromal cells seperated by compressed blood vessels.

All these different patterns may be found in different fields of the same tumor.

Another histological classification introduced by Silver and Hennigas, suggests that the cytoplasmic storage of lipid in stromal cells is an expression of age of the lesion. They finally defined 3 types[48].

Juvenile type : Contains sheet and columns of small cells coexistent with capillaries of various sizes, sometimes enlarged. There are a few or no xanthomatous cells. This type is preferentially observed in the first 3 decades of life.

Transitional Type : Due to the development of intratumoural microhemorrhages and transdution with formation of microcysts, in reaction to haemorrhage, endothelial cells enlarge using their phagocytic properties to capture erythrocytes and coagulated serum and they become swollen with a xanthomatous appearance.

Clear cell type : In this type the tumour is almost entirely made of xanthomatous cells. It is seen in the late stage in most advanced age catogories and is seen in recurrent cases.

It has been noted that these tumors are less well defind than the macroscopic appearance suggests. They grow without any capsule within the nervous system[49]. Reactive gliosis of the surrounding parenchyma is usualy pronounced and associated with penetration of astrocytic processes into the tumour.

Large number of mast cells are noted within the tumor as compared to the adjacent cerebellar tissue constituting a characteristic and significant histologic features [3,50].

2. Electron microscopy

First ultrastructural morphology of haemangioblatastoma was described by Cenncellà and Zimmarman in 1965[51]. Subsequently numberous studies have confirmed the same.

The major components constitute :

1. Capillaries with endothelial cells
2. Pericytes
3. Stromal cells
4. Mast cells
5. Extracellular space

Endothelial cells

They present frequent fenestration and contain numerous Weibel-Palade bodies, crystalloid bodies, and an increased number of small and large pinocytic vascular bodies[52] reflecting an active transendothelial transport and a high pathophysiological activity.

Pericytes : They lie immediately adjacent and external to the periendothelial basement membrane being themselves completely surrounded by a basal lamina.

Extracellular space : Contain scattered collagen fiberes,cell debris, granulofibrillary material and free lipid droplets.

Stromal cells :- are interspersed as a single cell or in group of a few cells in the loose intervascular space. They have a voluminous clear cytoplasm containing large lipid membrane bound inclusion, Whorls of laminated smooth endoplasmic reticulum are common.

Several reports pointed out the presence in the cytoplasm of stromal cells of membrane-bounded electron dense bodies measuring 120-300mm in dia meter suggesting secretary granules [53,54]. Some authors feel that they are representative of erythropoitic precussor substance [55].

Electron microscopy confirmed the presence of mast cells. They are preferently located at the site where the endothelial cytoplasm is attenuated and the vessel is devoid of pericyte covering. Mast cells are of two types [56].

1. Granules with dense particulate appearance.
2. Granules with crystalline substances.

Immunocytochemistry

Numerous studies are currently being performed. Their greatest preoccupation is elucidating the origin and nature of stromal cells.

Kepes at al., 1979[57] used immunoperoxidase method for detection of glial fibrillary acidic protein (GFAP) and in about 50% of cases, stromal cells were found negative for GFAP; in the remainder variable amounts of GFAP

were demonstrated. They then concluded that stromal cells may be heterogenous in origin, deposition of lipid droplets in cells of diverse origin may make them appear similar.

In 1982 Jure et al.,[58] used immunoperoxidase method for factor VIII related antigen and GFAP. All cases showed positive staining for VIII related Antigen in stromal cells and astrocytes staining positively for GFAP. But all stromal cell stained nagative for GFAP. They concluded that stromal cell are of endothelial origin and those identified by GFAP may represent stromal cells which have ingested reactive astrocytes within the tumor.

Tanimura et al, (1984) used immunoperoxidase technique for GFAP, S-100 and Factor VIII related antigen. They found that most stromal cells are GFAP positive and some S-100 and factor VIII R.Ag.stained negative except in endothelial cells lining the capillaries. They concluded that stromal cells consists of heterogenous cell population.

Frank et al., in 1989[60] used immunohistochemistry with 17 different cell type markers. No consistant staining of stromal cells for markers of endothelial, epithelial chromaffin or smooth muscle cell origin were noted. They concluded that stromal cells of haemangioblastoma do not arise from endothelial, neural, epithelial, percytic or neuroendocrine origin but are probably of undifferentiated mesenchymal origin.

The latest study in hypothesis of origin and nature of stromal cells are that conducted by Morii et al, 1993[61]. They studied using cell culture with in situ hybridization. They found that vascular endothelial growth factor (VEGF) mRNA were highly expressed in the stromal cells but not in the endothelial cells. So they concluded that VEGF secreted from stromal cells

plays an important role in endothelial cell proliferation in haemangioblastoma.

GENETICS

When haemangioblastoma occur as a representation of VHL complex then they are transmitted as an autosomal dominant trait with varying penetrance and it may be passed on by affected or unaffected members of either sex.

Using recombinant DNA technology,cytogenic analysis performed on families known to carry VHL gene indicated that VHL gene was localised to the short arm of chromozome 3. Seizinger et al., observed that the VHL gene linked with the homolog of the RAF1 oncogene, which was known to map to the specific segment of 3p designated 3p 25 [62]. Further cloning studies localised the gene to 3p 25-26 region. As progressively smaller segments were identified, the deleted segments were termed nested constitutional deletion. Eventually, the smallest of the identified nested constitutional deletions were searched with known probes from a c DNA for evolutionary conserved sequences. Two sequences designated g6 and g7 were then screened for VHL syndrome[62].The presents function of the gene product of g7 remains unkown. It is considered as a tumor suppression gene (A tumor suppressor gene function recessively and the VHL syndrome show dominant inheritant).

CLINICAL AND BIOLOGICAL DATA

I. Epidemiological and Aetiological Factors

A. Exogenous aetiological factors : Some reports in literature have indicated possible involvement of exogenous factors in the clinical appearance of haemangioblastoma..

1. Trauma

The head injury shortly before the onset of symptoms leading to the diagnosis of infratentorial haemangioblastoma has been present in a few cases[63,64,65].

2. Pregnancy

Pregnancy hastens the presentation of haemangioblastoma. Several reports in literature have cited detection of haemangioblastoma during pregnancies especially retinal [63,66,68].

Although increase in size of a haemangioblastoma during pregnancy is still controversial the fact that some patients improve spontaneously after delivery supports the probable role of vascular engorgement as a cause of tumor enlargement and decompression of symptoms by increased mass effect.

3. Familial

The incidence of familial cases ranges in literature from 5.3% (69) to 11.8% (5). The occurence of the disease in identical twins has been reported[70]

II. Sex

Males are more frequently affected than females. Male predominance is observed more notably in infratentorial and retinal locations. Ratio is 1.3%.

III. Age

Commonly haemangioblastoma manifest in adult life and the average age at diagnosis is 31.5 years for brain stem lesions, 32.3 years for supratentorial lesions, 34.9 years for cerebellar lesions and 36.5 years for spinal lesions[39]. Presentation before 10 years & after 65 years are rare.

Table VII - Sex distribution

Series	Male	Female
Jamisson et al (1974)	14	4
Jeffneys (1975)	44	23
Olivecrona (1952)	41	29
Palmer (1972)	50	30
Papo et al (1961)	27	17
Robinson (1965)	11	12

The youngest patient in Matson series [71] is 12 years , Olivcrona series[72] 10 years Mondkar et al [73] is 4 years. Three examples of congenital haemangioblastomas were reported, two with cerebellar location responsible for the death of a new born in the course of delivery[74] and of an infant at day seven[75].

The oldest patient in literature to present with haemangioblastoma was 82 years for an infratentorial haemangioblastoma[30]. Haemangioblastoma presents earlier in females than in males[72]. Haemangioblastoma present in VHL disease and familial forms much ealrier than in sporadic cases[5] . Mean age at diagnosis in familial cases[5] is about 5.6 years earlier than sporadic.

The peak incidence is in the third decade with a second peak in the fifth decade.

IV. SIGNS & SYMPTOMS

The average duration of symptoms is 13 months with a range from 3 week to 7 years. The signs and symptoms vary to certain extent, depending on the precise location of the tumor.

Posterior fossa

Headache is the most common initial symptom present in incidence ranging from 90%[73] to 93% [76].At the time of admission other signs of raised ICP are present nearly 100% of the time[77]. Giddiness, ataxia was present in 51.2% and gait disturbance 36.4% [5]. Papilloedema is present in various proportion ranging from 56% to 90% [72]. In the French society of neurosurgery series[5], normal neurological examination was seen in 14.3%cases. A single or combined neurological disorders in 87.3% of cases such as, hemispheric cerebellar signs, central vestibular syndrome,vermian signs,pyramidal sign,imparied consciousness, brain stem signs etc were found.

Spinal haemangioblastoma

Spinal pain is the most common presenting symptom and is a reliable indication of level of the tumor[78,79]. Next most common symptom is spastic quadriparsis and other features of tumors.

Retinal haemangioblastoma

Retinal haemangioblastoma progressive loss of vision or ocular pain lead to ophthalmic examination and fundscopy reveal the diagnosis.V.

V. Biological Characteristics

Secondary erythrocythaemia

There is only an increase in RBC count with a parallel increase in haematocrit, haemoglobin and blood mass accompanied by bone marrow erythro blastosis at marrow examination. Such an increase is probably due to production of erytheropoisis stimulating factor a hypothesis formulated by Ward et al., in 1956[80].

It was first reported in 1933, Carpenter et al.,[81] who reported 2 cases of polycythemia and suggested a diencephalic origin for stimulation of an erythropoietic center rather than an aetiological factor related to tumoural type.

Production by Retinal haemangioblastoma of an erythiopoeses stimulating factor was demonstrated for the first time in 1961 by Waldmann et.al.,[82] when they successfully tested in vivo the erthropoietic activity of urine, plasma, CSF and cyst fluid of a patient with recurring haemangioblastoma.

The secondary polycythemia disappeared once the haemangioblastoma was totally removed, also strongly suggesting a factor of tumoral origin.

IV. Diagnosis Imaging

C.T.Scan

Demonstrates the neoplasm and other associated features, It is predominantly isodense before contrast and enhances markedly on contrast

admnistration. Tumoral cyst is hypodense. Solid tumors may be slightly hyperdense and brightly enhances with contrast. Sometimes some vessels supplying the tumor can be seen as linear enhancing structures.

MRI

Currently MRI is the imaging modality of choice. MRI demonstrate low signal on T1 weighted images and high singal on T2 weighted images. Adminstration of contrast demonstrates intense enhancement of the mural nodule. Solid tumors enhance homogenously on contrast adminstation.

Spinal cord haemangioblastomas are chracterised by an intramedullary vascular nodule with enlarged draining veins, diffuse enlargement of the cord or as an intramedullary cyst [78]. The imaging characteristics are same as that in the brain.

Angiography

The first report of angiographic demostration of an infratentorial haemangioblatastoma fed by vertebral artery was by Lindgren[83]. Four different vascular patterns are noted.

1. A vascular mural nodule with in an avascular cyst.
2. A doughnut ring of abnormal vessels surrounding an avascular space representing an intratumoral cyst.
3. A large solid vascular mass.
4. Multiple small, widely separated vascular nodules.

It is especially useful in detecting spinal lesions as well.

II. Disease Assesssment

It has been noted that there is a high risk of multiple tumour in both sporadic and familial forms of haemangioblastoma. It is important to screen an affected patient to rule out lesions at other situations and also to label them as part of VHL complex or otherwise. For this a screening protocol has been deduced.

1. Basic check up

- Neurological examination
- Fundus examination
- Somatic examination
- Blood counts
- Biological investigations
  - ➡ 24 hrs urinary total catecholamine and VMA levels.
  - ➡ Plasma epinephrin and non epinephrin levels.
  - ➡ Familial inquiry

Complementary check up

- Detection of retinal Retinal haemangioblastoma. If ophthalmoscopy is doubtful follow with fluoresein angiography.
- Detection of brain haemangioblastoma. C.T. without and with contrast, if doubtful, MRI with contrast, if positive DSA prior to surgery.
- Spinal cord screening
  - ➡ MRI if positive, DSA prior to surgery
- Detection of Visceral lesions
  - ➡ Scintigraphy (^{123}I or ^{131}I-MIBG)
  - ➡ Abdominal USG if doubtful or positive abdominal C.T. Scan/ MRI, if necessary DSA (selective renal)

TREATMENT

The only efficient treatment for haemangioblastoma is total surgical excision.

In macrocystic haemangioblastoma the cyst is partially decompressed, the subpial mural module is visualised, the suppling vessels are controlled and the cyst wall totally excised.

In solid haemangioblastoma (type 3,4) preoperative embolisation if necessary is advocated and total excesion with progressive meticulous control of supplying vessels by coagulation is advocated. Such tumors must be removed as a single mass. Torrential haemorrhage may occur if the tumor is transected.

Excision of spinal cord hemangioblastoma requires mirosurgical technique. Preoperative (Gd-DTPA) enhanced MRI and spinal angiography are necessary (embolisation if necessary) as advocated by Friedrich H. et.al.[34] Ultrasonographic peroperative localisation is recommended by Isu T. et.al.[85] and Sanders W.P. et. al.[86]. During tumor dissection one must remain out side the nodule with a progressive course in a loose cleavage plane created between the tumor and the cord. Transection of the cord must be avoided.

Retinal haemangioblastoma : - photocoagulation with xenon arc was the first positive treatment with favourable results as reported by Meyer Schwickerath et al.,[82]. The latest method is endocular surgery and eye wall resection as advocated by Peyman et al., in 1988[88].

Radiotherapy

Earlier, radiotherapy was advocated as palliative modality in multiple lesions or as pre-operative adjuvant therapy for highly vascular haemangioblastoma. Radiotherapy is also indicated when only biopsy was performed and after recurrence. 1400 and 6000 rads has been advocated for 4-5 weeks period. An increase in tumoral volume has been noted to be 15-55%. (Helle et al., 1980 Smally et al., 1990[89]).

RESULTS

The post operative mortality for single lesion after total excision varies from 8.3[65] to 16.3% [5]. Mortality is higher with macroscopically solid form (type 3 and 4) than with macrocystic haemangioblastoma (type 2)[5]. Spinal cord haemangioblastoma as reported by Harth et al., have a 76% good results after total excesion[65]. The mean survival was 90% at 5 yrs 80% at 10 yrs and 40% at 20 years. The recurrence is 12.25% and recurrence as late as 24 years have been recorded[65].

The favourable factors are solitary lesions, type I and type II, no associated familial history, absence of extraneuroaxial lesions, and retinal lesions.

The unfavourable factors are early age of presentation associated familial history, multiple leisons and associated complex lesions.

OBSERVATIONS AND RESULTS

41 conservative cases of haemangioblastoma surgically treated at SCTIMST over a period of 20 years from 1977 to 1997 were retrospectively analysed. The age group ranged from 17 years to 60 years table 1.

Table 1 : Distribution of patients in age group

Age group Year	Cranial	Spinal	VHL	Total (%)
01-10	-	-	-	-
11-20	2	2	2	4
21-30	12	3	4	15
31-40	14	1	5	15
41-50	3	-	-	3
51-60	4	-	-	4
61 >	-	-	-	-

Majority of the patients were in the 3rd and 4th decade of life with spinal and VHL more common in the 2nd 3rd decade. There was a definite male preponderance with 29 out of the 41 being males and the rest being females (Table 2).

Table 2 : Distribution

Sex	Cranial (%)	Spinal (%)	VHL Complex (%)
Male	25 (60.9)	3 (7.3)	7 (17.00)
Female	10 (24.3)	3 (7.3)	4 (9.7)
Total	35 (85.3)	6 (14.6)	11 (26.8)

Out of the 11 VHL complex patients again there was a male preponderance (7 out of 11). In spinal the male female ratio was equal.

Analysis of the clinical presentation of these patients were broadly classified as in Table 3.

Table 3 : Modes of presentation

	Cranial	(%)	Spinal	(5%)
1.	Raised ICP features	32 (73.04)	Motor deficit	4(66)
2.	Cerebellar signs	13 (31.7)	Sensory deficit	1 (16)
3.	Brain stem / cranial nerve deficit	2 (4.8)	Incidental	1 (6)

From table 3 it is evident that most of the patients (73.04%) presented with features of raised ICP especially in the form of headache and vomiting. 39 of the 41 patients (95%) had papilloedema. Cerebellar signs were also a significant finding at presentation. In the spinal group most patients, had either sensory or motor deficits with motor predominating. One of the spinal cord lesion was incidentally found while working up for cranial symptoms. There are 11 cases which qualified the criteria for VHL complex (Table 4).

Table 4 : VHL complex analysis

	Percentage (%)
More than 1 lesion	7
Family history	2
Associated lesion	-
Retinal angioma	4
Abdominal Lump	1

Out of the 11 patients in the VHL group were in the 3rd and 4th decade. 7 patients had more than 1 lesion in neuraxis and four of them had retinal angiomatosis.

Table 5 : Distribution of tumor in CNS

Cranial 35 (85.3%)		
Cerebellum	Hemisphere	23 (65.7)
	Vermain / para vermian	10 (28.5)
	Tonsil	1 (2.8)
Sphenoid sinus		1 (2.8)
Spinal		6 (14.6)
Cervical		4 (66%)
Cervicodorsal		1 (16%)
Dorsal		1 (16%)

34 of the 41 patients had lesion situated in the posterior fossa; majority of the patients (23) had hemispheric tumors with more or less equal distribution of sides. One of them were exclusively within the tonsil. In 10 (28.5%) the lesion was in the vermis or paravermian areas.

We had one case where the tumor was situated in the sphenoid sinus. In the spinal cord haemagioblastomas, four were situated in the cervical region with one each in the certicodorsal and dorsal regions.

Preoperatively 16 out of the 41 patient had polycythemia (Hb) > 15g% and PCV>45%). Biochemical tests for the estimation of catecholamines and VMA levels were not performed.

Radiology

All patients underwent CT scan and angiogram scan was performed in 18 patients. Preoperative embolization was carried out in one patient. The lesion were classified based on imaging as:-

Type I- Cystic
Type II - Cystic + solid
Type III - Only solid (Table 6)

Table 6

Type	Cranial	Spinal	Total (%)
Type - Cystic	1	0	1 (2.4)
Type II - Solid + Cystic	19	3	22 (53.6)
Type II - Solid	15	3	18 (4.39)

Out of the 18 patients who underwent angiogram, three had normal study. Majority of the feeders were from PICA followed by AICA and anterior spinal artery. One dorsal lesion had supply from D9 intercostal artery.

TREATMENT

Preoperative V.P.shunt was performed in 20 of the 41 patient. One patient had post operative V.P.Shunt. The surgical procedure consisted of either subtotal or total excisions (Table 7).

Table 7

Procedures	No.of patients	%	Total %
CSF diversion	22 (1 postop.)	62.8	-
Tumor Excision	Cranial	Spinal	
Total	32 (82.7)	5 (83.3)	34 (82.9)
Sub total	2 (17.1)	1 (16.6)	1 (17)
Not removed	1	-	-

Five out of the 35 initial cases died following initial surgery. Out of the five who had recurrence four underwent revision surgery and two of them died. No mortality for spinal lesions were noted at initial surgery. One patient was operated twice 2 years and 4 years after initial surgery and died following the third surgery.

OUTCOME AND FOLLOWUP

The assessment at discharge and on followup were based on the Glawsgo outcome score. 16 patients had frank cerebellar sings, 6 patients had only gait ataxia. One of them had a non functioning eye at discharge. Thirty of the thirty five cases were on regular followup. Fifteen of them were grade I at discharge and 10 in grade II, there were one each of grade III

& IV. Twenty five of the cranial are in subsequent regular followup & five of thirty had recurrence. Four of them were reported out of which 2 died. The other two are still on long term followup. The operated cases one of the was operated 4 times and the other 3 times and are in grade II and III at present.

Table 8
Mortality for initial surgery & Recurrent surgery

	Total No.		Died	
	Cranial	Spinal	Cranial	Spinal
Initial surgery	35	6	5	0
Recurrent Surgery	4	1	2	1

Therefore the mortality for initial surgery (i.e. out of 35 cases 5 died) is (1%) and with revision surgery is (2 out of 4) 50%. At latest followup the following is the out come. Fifteen patients were in grade I, ten in grade II and one each in grade III & IV. Of the spinal cases one of the them is in grade I, 3 in grade II and in grade IV (Table 9).

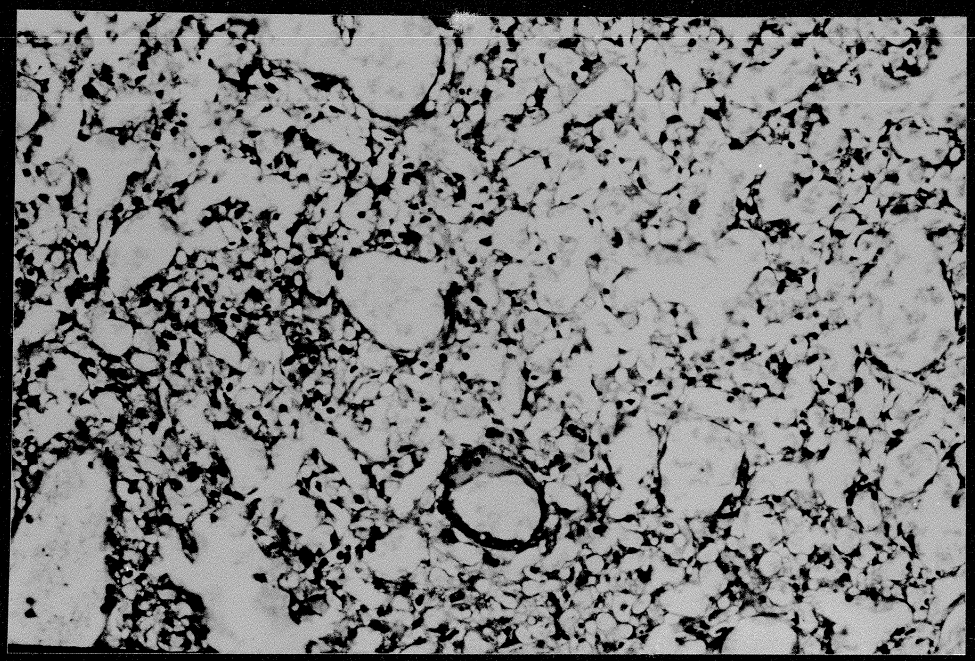
Grade	Cranial	Spinal	Total%
Grade I	15	1	16 (39)
Grade II	10	3	13 (31)
Grade III	1	2 (4.8)	
Grade IV	1	Nil	1 (2.4)
Expired	8	1	9 (21.9)
Total	35	6	41

On correlating C.T.Scan and type of lesion (Table 10) it is observed that mortality was more in type III and recurrence in type II & III.

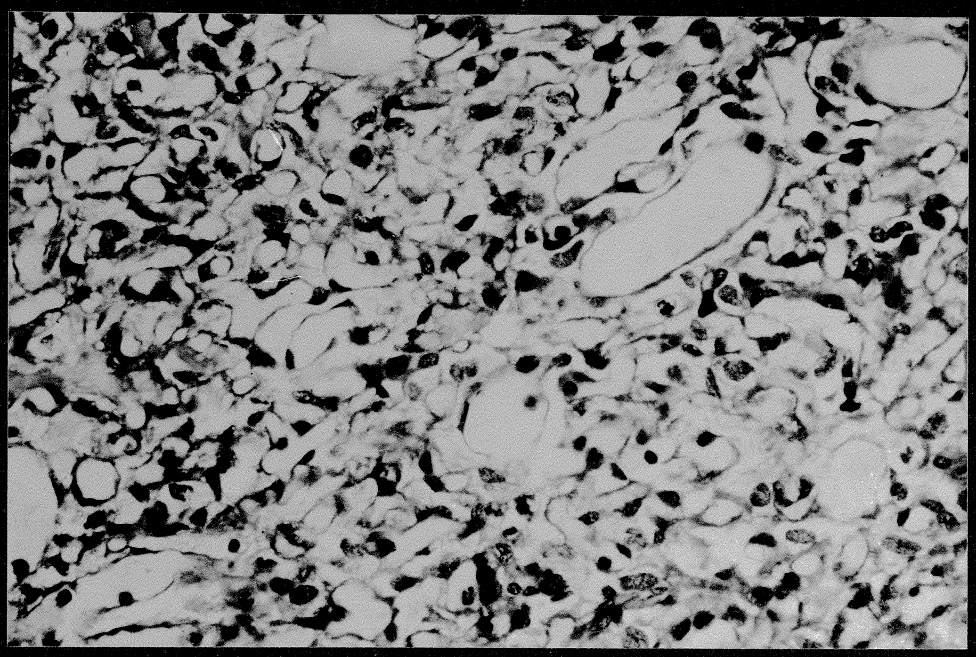
Table 10

C.T. Scan Type	No.of Patients %	Recurrence	Death
I	1 (2.4%)	-	-
II	23 (53%)	2 (9%)	2 (9%)
III	18 (43%)	2 (11%)	7 (38%)

HISTOPATHOLOGY

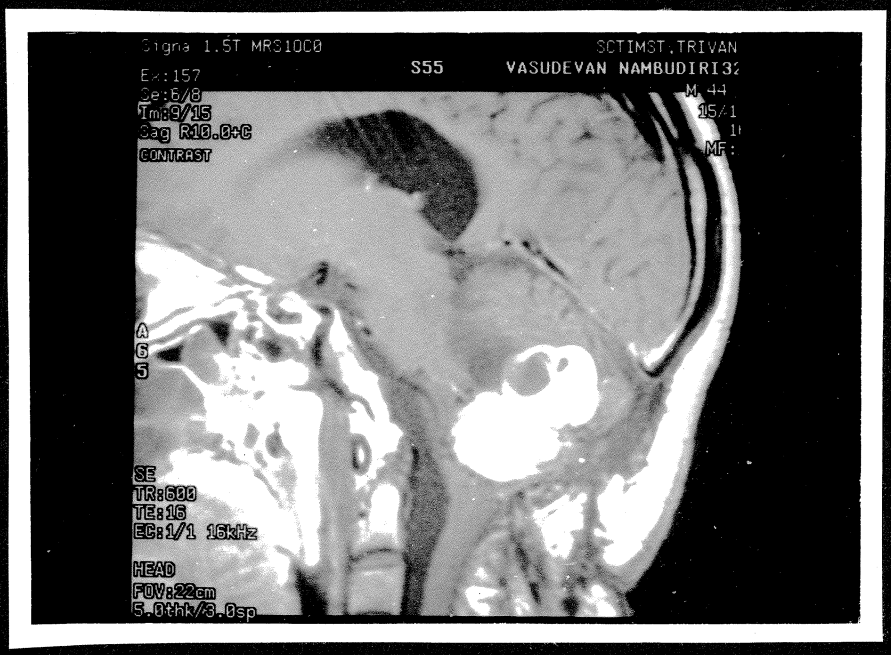


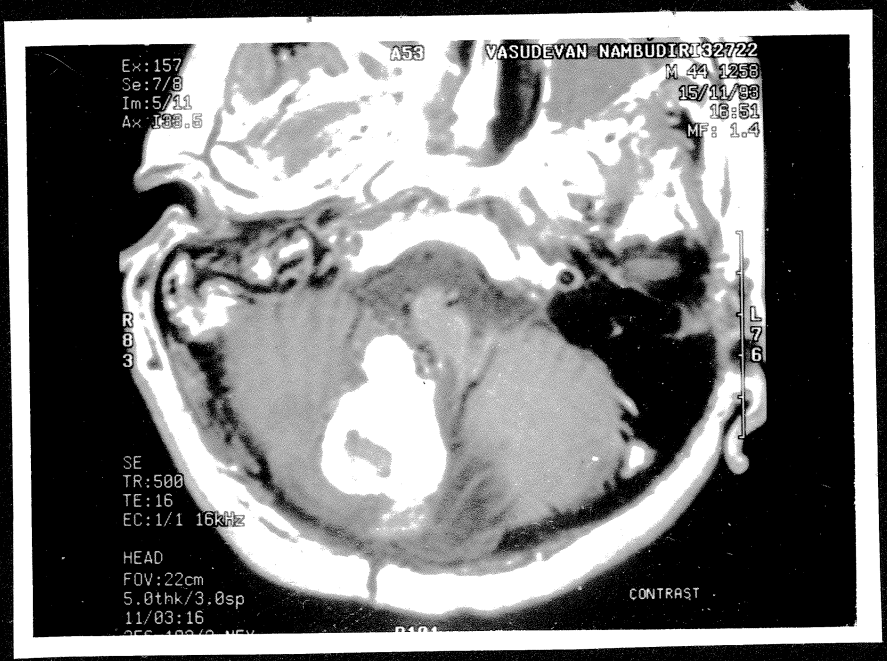
LOW POWER



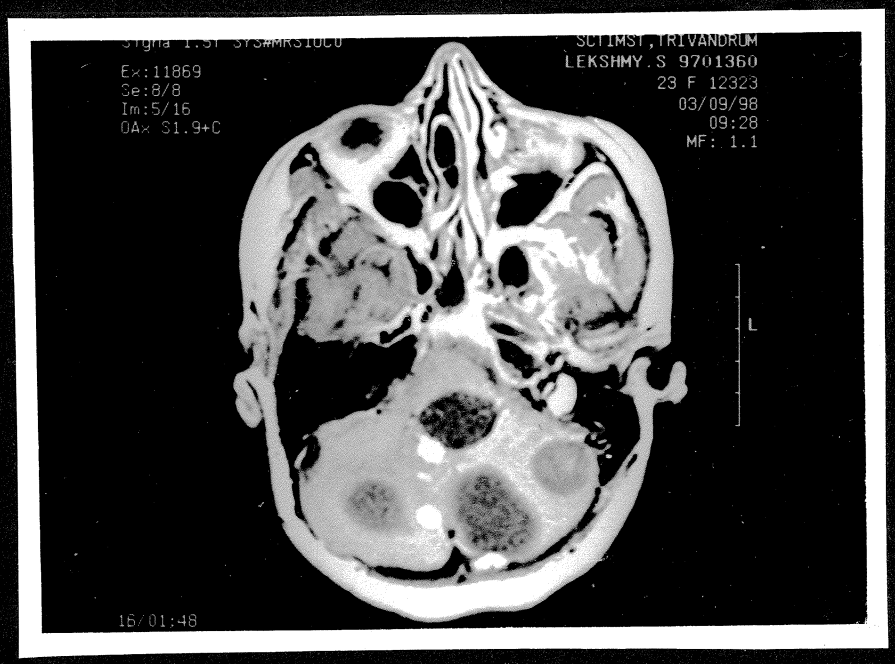
HIGH POWER

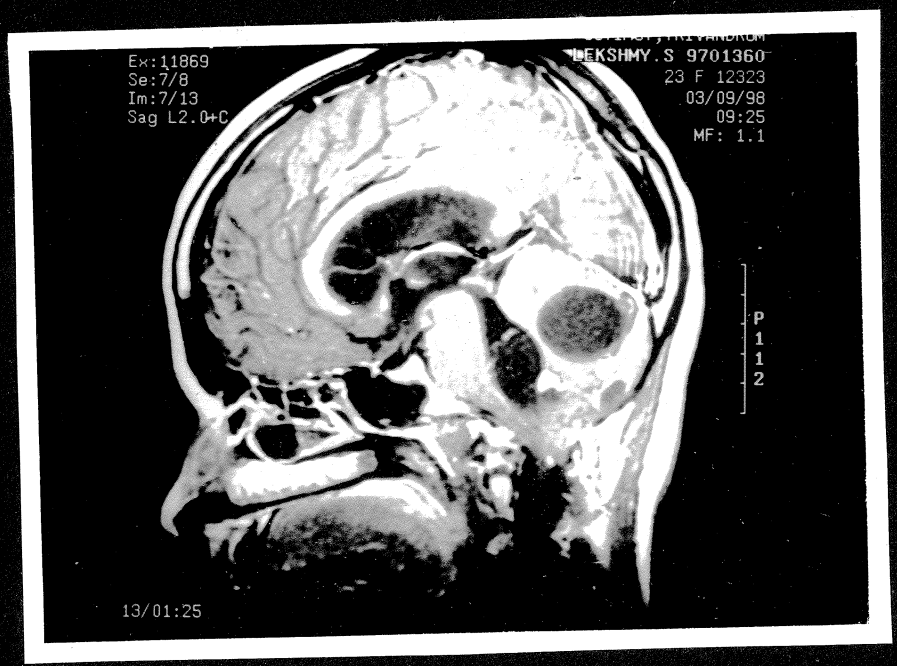
SOLID HAEMANGIOBLASTOMA WITH CYSTIC COMPONENT



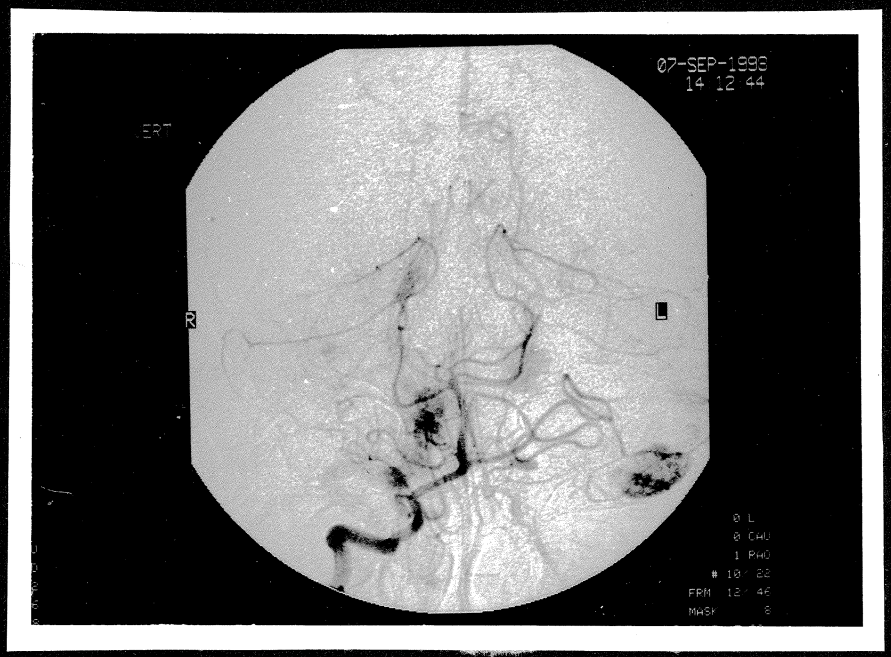


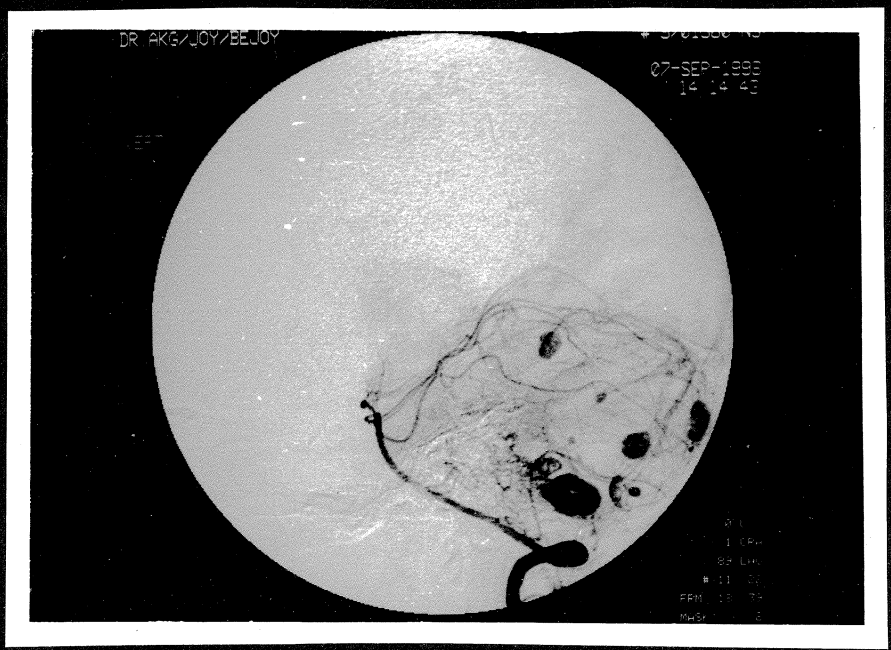
CYSTIC HAEMANGIOBLASTOMA WITH MURAL NODULE





DIGITAL SUBSTRACTION ANGIOGRAPHY
MULTIPLE CEREBELLAR HAEMANGIOBLASTOMA





DISCUSSION

The present study of 41 cases of CNS haemangioblastoma is a retrospective analysis of patients seen over 20 year period from 1977 to 1997. The study being a retrospective study has got certain obvious disadvantages. As strict protocol was not followed in management of these patients, all required investigations were not performed in all patients. Neuropathalogical and haematological investigations were done in all patients, none had biochemical screening of catecholamines and chromosomal studies. Ultrasound examination was performed in most patients especially in the later part of the study. Eighteen patients underwent angiographic study and MRI was performed in seven patients.

In the present study, there was a definite male preponderance male:female ratio being 2:1. This is in confirmation with various other reports (Jeffrey R 1975, Neuman M and Melmasm KL 1972, Mondkar et al 1976, Palmer JJ 1972).

Jeffreys et al (1975) have quoted that hemangioblastoma is a disease of middle age between 3rd and 5th decade of life. In this study also majority of the patients belonged to the 3rd and 4th decade (78.7%). The youngest patient in this study was 14 years of age and the oldest 60 year of age. In literature haemangioblastomas have been reported in extremes of age groups. Congenital hemangioblastoma (Roig et al 1988) and haemangioblastoma at 89 years of the age have been recorded (Laborde 1991).

In our study one patient had bilateral retinal angioma of which one eye was non functional and the other eye was treated by photocoagulation and had intact vision. This patient qualified as VHL complex. Similarly we had seven patients with more than one lesion in the neuraxis and two of them also had a positive family history. Similar observations have been reported in literature/Newman 1972 Resche et al 1983). A total of eleven cases have been found to qualify as VHL syndrome (26.8%).

Posterior fossa is the most favoured site of tumor and accounted for 85.3% in our study and the quoted in literature in 92.6% (Myens et al 1961, Newman and Helman 1972). In our study we had one case of haemangioblastoma in the sphenoid sinus and another in the temporal lobe. In literature Ferrite et al 1984 reported 3 cases among 5991 intracranial tumors (0.5%). A recent review of literature by Ferranle et al in 1988 listed 71 cases of supratentorial haemangioblastomas.

Spinal haemangioblastoma in our study constituted 6 (14.6%) land cervical region was the commonest site (66%).

Polycythemia was present in 16 out of the 41 patients. Polycythemia has been described to occur in 35.40% of persons harbouring haemangioblastoma (Bohling et al 1987).

C.T.Scan is diagnostic with associated polycythemia and other visceral lesions. In those with mural nodule, the diagnosis of haemangioblastoma is an high as 100% (Palmer JJ 1972). In cystic lesions a diagnosis of cystic astrocytoma/cystic tuberculoma was also entertained. But intra-operatively

postoperative mortality after total excision in solitary intracranial lesions ranges from 8.3 to 16.3 (Palmes et al 1972, Resche et al 1993).

Decompressive procedures are associated with high postoperative mortality rate of 26.3% to 35% (Resche et al 1983). In our series the operative mortality was 21.9% majority of the patients 7 out 9 (77.7%) who died has solid haemangioblastomas. There was a 9% mortality in solid with cystic tumors were as in solid tumors the mortality was 38% of total. Recurrence was seen equally with both type II and III (2 each). On followup one patient had recurrence 5 times another had recurrence 3 times and one twice.

The overall outcome of patient in grade I 39% and grade II was 31%, grade II and IV were 4.8% and 2.4%. All patients at followup had no recurrence of tumor. On reviewing literature the recurrence ranges from 12 to 25% (Mondkar et al 1967,Palmer JJ 1972). The outcome at last followup of a total of 15 patients, 12 of them were in grade I, 2 of them in grade II. One patient was severely disabled, grade III.

the diagnosis was definite in view of the red and angry looking lesion without a connective tissue capsule and good plane of cleavage.

MRI reveals low signal of T1 weighted images and high intensity signal on T2 weighted images (Asan et al 1992,Resche et al 1983). MRI is the imaging of choice as it free from bony artifacts and also reveals multiple and occult lesions (Asan et al 1992). MRI was done in 7 patients in the later part of the study.

With the advent of MRI, angiography is less in use for diagnosis. But gives a idea of the major feeder and if necessary one can also plan for preoperative embolization (Lindgren et al). It also helps in finding occult spinal lesions.

It has been suggested that only effective treatment of these belong lesions is a total excision (Yasargill 1976, Djindjian 1986). The tumor has not limiting connective tissue capsule but has good plane of cleavage. The tumor has to be circumscribed during surgical excision and decompression or biopsy is often associated with uncontrollable haemorrhage.

Preoperative embolization has been recently advocated in tumors with major feeders as it has been found to reduce intraoperative bleeding, it is however, not the substitute for circumscribed total excision (Handraj et al 1994, Tampeiri et al 1993). In the present study only one patient underwent preoperative embolization for a left cerebellar solid haemangioblastoma with PICA as the feeder. He had a grade I outcome.

It has been observed that post operative mortality is high in solid hemangioblastomas (Djindjian 1986, Lindsay Sinmon and Murato 1993). The

CONCLUSION

- Hemangioblastoma is a benign vascular tumor and is rare.
- Familial and genetic types are encountered.
- 3rd and 4th decade occurrence common.
- Male predominance is noted.
- Posterior fossa is the commonest location.
- In spinal cord commonly seen in intramedullary location.
- Raised ICP features commonest presentation.
- MRI is the imaging of choice.
- Total excision is the treatment of choice with cure.
- Solid lesions are more associated with poor outcome.
- Good outcome if totally excised.
- Reoperation increases morbidity and mortality.
- Overall prognosis good.

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