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PROJECT REPORT

Name : ***DR. Rajesh B J***

Programme : ***M.Ch. NEUROSURGERY***

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TITLE OF THE PROJECT:

CLINICOPATHOLOGICAL STUDY OF CERBRAL ANEURYSMS

Name	:	*DR. Rajesh B J*
Programme	:	*M.Ch. NEUROSURGERY*
Month and Year of Submission	:	*NOVEMBER - 2001*

CERTIFICATE

I, Dr. Rajesh B J hereby declare that I have actually performed/assisted all the procedures listed under report.

Place: Thiruvananthapuram

Signature:

Date : 1stNovember – 2001

Name in capital letters
(Rajesh B J)

Forwarded. He has carried out the minimum requirement of procedures / etc.

Signature

Prof. R.N.Bhattacharya
Head of Department of Neurosurgery
SCTIMST , Thiruvananthapuram-11

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Rajesh B J

CONTENTS

Preface

PREFACE

Cerebral aneurysm is one of the most alarming conditions known to mankind and it carries considerable mortality and morbidity. Management of cerebral aneurysms is a surgical challenge. Statistics reveal that there has been an increasing incidence in referral of cerebral aneurysms to our institute over the last decade. Cases of mycotic aneurysm have been reported from our institute earlier, but for a large number of cases the etiopathogenesis of cerebral aneurysms has not been studied so far. This prompted us to undertake a clinicopathological study on such aneurysms. The aneurysm sacs were excised after clipping and examined histopathologically. The results were analyzed and correlated with the clinical features. The study showed mucoid degenerative changes in a significant number of specimens along with hypertension and smoking as important risk factors. Similar mucoid degeneration has been reported in both intracranial and extra-cranial aneurysms from elsewhere in the world, with most of them being case reports.

This study documents for the first time, a detailed histopathological study of aneurysms excised from a large number of patients and provides important evidences regarding the nature of the aneurysms and the possible role of dietary factors in their etiopathogenesis, besides known risk factors. There is a need to identify serological markers and noninvasive techniques of diagnosis and to evaluate the dietary and other risk factors for cerebral aneurysms. These studies will help to develop appropriate therapeutic and preventive methods.

Introduction

INTRODUCTION

There is an increasing incidence of cerebral aneurysms being operated on at our institute over the last decade. Besides mycotic aneurysms[1,2,3], a large number of cerebral aneurysm cases with no definite cause were encountered at Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), during the last 25 years. Although clinical aspects of cases operated upon were reported earlier[4], a detailed histopathological study was not carried out on them and studies to ascertain the probable aetiological factors were not undertaken so far.

Preliminary studies indicated the occurrence of mucoid degenerative changes in the aneurysm wall, similar to mucoid vasculopathy, identified by Sandhyamani as a distinct diet induced vascular connective tissue entity in Kerala, resulting from nutritional imbalance with low-protein high-starch diets[5,6,7]. A clinico-pathologic study was conducted to ascertain the nature of the histopathological lesions and associated risk factors in cases of cerebral aneurysm admitted at SCTIMST, Trivandrum, during a 2-year period.

Aims
&
Objectives

AIMS AND OBJECTIVES

The aims and objectives of the present study are

- Histopathological study of excised cerebral aneurysms
- Analysis of clinical data
- Clinicopathological correlation

Materials and Methods

MATERIALS AND METHODS

During the two-year period from Jan 1999 to Dec 2000 a total of 255 cases of cerebral aneurysms were operated on. The present study was conducted on 57 of these cases where the aneurysm sac could be excised and subjected to histopathological study. The study did not include cases of mycotic aneurysm nor those due to inherited connective tissue disorders. The patients taken into the study were analyzed by using Glasgow coma scale and world federation of neurological surgeons scale on admission. All the patients included in the study were in good grade. Clinical parameters including the age, sex, economical status, the risk factors modes of presentation and the radiological data were taken into consideration for analysis.

Aneurysm sacs removed after clipping, were fixed in 10% buffered formalin, processed through graded alcohol and embedded in paraffin wax. 5μ thick sections were examined, using hematoxylin and eosin, Verhoeff van Gieson's and toluidine blue staining techniques. Histopathological observations were analyzed and correlated with clinical features of these patients.

Review of Literature

Review of literature

The word "*Aneurysm*" is from the Greek word "*aneurysma*" which is derived from '*ana*' meaning across and '*eurys*' meaning broad. It is described as a localised and persistent dilatation that results from the yielding of the components of the wall of the heart or blood vessels.

Aneurysms of the central nervous system are classified as follows[20].

•Histologically as true and false aneurysms

True aneurysm: Is the one that is formed by the dilatation of the components of the vessel wall.

False aneurysm: Is the one resulting from rupture of a vessel where the pulsatile hematoma so formed is walled off by organizing granulation tissue and neighboring tissues.

•Anatomically (morphologically) as saccular, fusiform and dissecting

Saccular (berry) aneurysms: These are eccentric sac like dilatations from the vessels wall with a well-defined neck.

Fusiform aneurysms: These are ectactic dilatation of the vessel wall without a well-defined neck and involve the full circumference of the affected vessel.

Dissecting aneurysms: These aneurysms occur due to dissection of blood into the wall of the blood vessel.

•Etiologically as Congenital or Acquired.

Saccular aneurysms: Saccular aneurysms are the commonest type of intracranial aneurysms responsible for subarachnoid hemorrhage. Curiously, a slight predominance of females has been found in all reported series. Multiple aneurysms are found in nearly 25% of cases.

Berry aneurysms vary in size from pinhead to several centimeters in diameter. Small aneurysms have extremely thin walls. In larger aneurysms the sac itself often becomes partially or completely filled with organized laminated thrombus and the variations in the wall thickness may result in multilocular aneurysm, which is more susceptible to bleeding.

MICROSCOPIC APPEARANCE:

In a detailed study of berry aneurysm, it was found that they commenced as areas of mural thinning with fragmentation and loss of internal elastic lamina, progressive attenuation and disappearance of the media and thinning of the adventitia[24]. These could be recognized macroscopically as areas of thinning with or without mild dome like or funnel shaped dilatation. Microscopically the wall of the aneurysmal sac varies in thickness and consists of thin layer of fibrous connective tissue or the adventitial layer, which is continuous with the adventia of the parent vessel. The muscular layer may end abruptly at the neck of the aneurysm or may be fragmented in the wall of aneurysm, and the internal elastic lamina is either fragmented or reduplicated and the normal fibrillary structure may be lost. At the site of the rupture, the elastic tissue is totally absent. In other areas of the wall of the aneurysm the elastica may be thickened and beaded in appearance. The sac is lined by organizing mural thrombi or fibro-calcific plaques. Presence of hemosiderin-containing phagocytes is indicative of previous leakage.

PATHOGENESIS:

The pathogenesis of saccular aneurysms is controversial, and currently two opposing views are held. These propose on the one hand congenital and on the other acquired factors in the development of saccular aneurysms. It is known that cerebral arteries differ from extra cranial vessels in the absence of external elastic lamina. The media and adventitia are very thin and contain only a few fibrils of elastic lamina. The intima consists of well-developed internal elastic lamina that separates the intima from media. Since the vessel wall maintains its integrity by both the internal elastic lamina and media, for an aneurysm to develop both of these should give way, but most accept that the internal elastic lamina is the most important layer for the integrity of the vessel wall. The considered view is that the interplay of various hemodynamic parameters, the vessel wall composition and underlying connective tissue protein metabolism are responsible for the development of saccular aneurysms[24].

More specific factors that have been cited as being associated with the two pathogenic mechanisms are listed below.

•Congenital factors.

1. Defect in the muscular layer
2. Failure of involution of fetal vessels

•Genetic factors and familial aneurysms

•Acquired factors

1. Atherosclerosis
2. Hypertension
3. Smoking
4. Inflammation

Congenital Factors:

The coexistence of congenital abnormalities with berry aneurysms was long used as evidence for the congenital theory until statistical analyses indicated that the association was not significant. However it is generally considered that the association of coarctation of aorta or polycystic disease of the kidneys with berry aneurysms is more frequent but hypertension is usually associated with both these congenital diseases and may precipitate aneurysm formation.

Some of the well-known theories for congenital origin are as follows[24].

The Medial Defects: Cerebral arterial walls have defects in the muscular layer at points of bifurcation. Developmentally, the muscle sheath of an artery derives from undifferentiated mesenchymal cells. These surround the branches and the parent vessels independently and are discontinuous at the branching points. Forbes termed these defects 'Locus minoris resistentiae". Eppinger first recognized these defects and suggested that herniation of the intima through this gap was responsible for aneurysm formation. However Stehbens has shown that medial defects were acquired in origin, are no more than adventitial raphes and demonstrated that they increase in frequency with age and thus their involvement in the causation of aneurysm is fortuitous [24].

Failure of involution of primitive vessels and variations in circle of Willis: The location of aneurysms coincides with the site of the primitive vessels and incomplete involution or atrophy of these arteries has been postulated as the cause of aneurysm formation. Although anterior communicating artery aneurysms coincides with the site of the primitive circle of

Willis, the anatomical variations are not found significantly more in patients with aneurysms as noted by Stehbens[24].

Genetic factors and familial aneurysms:

Collagen and elastin are the two fibrous connective tissue proteins responsible for the strength of the blood vessel wall and it is therefore natural that connective tissue disorders associated with vascular fragility may predispose to cerebral aneurysm. The rarity of cerebral aneurysms in infancy and childhood disputes a congenital origin[24].

Numerous heritable connective tissue disorders have been associated with intracranial aneurysms, including Polycystic disease, Ehlers-Danlos syndrome, Marfan's syndrome, Neurofibromatosis type 1, Osteogenesis Imperfecta, Pseudoxanthoma elasticum and Alpha 1 Antitrypsin deficiency. It is not known to what extent these specific heritable disorders contribute to the formation of intracranial aneurysms in the population. In addition the family history may be negative because the disease can be caused by a new mutation. Nevertheless the identifiable heritable connective tissue disorders contribute to a relatively small percentage of intracranial aneurysms.

ACQUIRED FACTORS

***Degeneration of internal elastic lamina*:** Forbus et al in a series of experiments suggested that the elastic lamina, which gives significant strength to the vessel wall, degenerates due to mechanical factors and leads to aneurysm formation. It has been shown that smoking and hypertension affect the internal elastic lamina and lead to weakness of the vessel and aneurysm formation[10]. Histologically, cerebral arteries contain three layers: an outer collagenous tunica adventitia, a muscular tunica media and a tunica intima lamina lined by endothelial cells. The media and adventitia are very thin and contain only a few fibrils of elastica. The intima consists of well-developed internal elastic lamina that separates the intima from media. The external elastic lamina is absent. Compared to extra cranial arteries the intracranial vessels are more susceptible to aneurysm formation attributable to lack of external elastic lamina. The mechanical properties of the arterial wall are mainly determined by elastin, collagen, the elastin - collagen ratio and smooth muscle cells. Thus changes in composition and structure of arterial wall will alter its mechanical properties.

***Preaneurysmal lesions*:** These are the small infundibular dilatations of the vessel wall with size less than 3 mm. Stehbens noted funnel shaped dilatations at the origin of the posterior communicating artery in 10% of autopsies studied. Gradations of these dilatations to actual small aneurysms were also found, suggesting that the dilatations represented the stages in the development of aneurysm formation. Patrick and Appleby demonstrated angiographically that these infundibular dilatations lead to the formation of aneurysms, but

no specific histological abnormalities were seen. However it is now considered that these infundibular dilatations do not lead to the formation of cerebral aneurysms.[15]

***ATHEROSCLEROSIS*:** The role of atherosclerosis in the formation of cerebral aneurysm is controversial. Carmicheal proposed a combination of developmental defects and atherosclerosis in the genesis of aneurysms. Frank generalized atherosclerosis is occasionally associated with fusiform dilatation of vertebral, basilar and internal carotid arteries. However the present consensus is that atherosclerosis does not lead directly to formation of aneurysms[15,25].

***HYPERTENSION*:** Numerous clinical, experimental and autopsy studies have strongly suggested that systemic arterial hypertension is an important risk factor in the development of intracranial aneurysms. [12] The mechanisms described are:

1. **Endothelial injury**: Endothelial injury has been considered as the initiating event in the formation of aneurysm. Hypertension is the most important cause of endothelial injury and is associated with morphological and functional changes in the endothelium. Morphological changes include a subendothelial accumulation of fibrin and cellular infiltration, together with swelling of the endothelial cells. Hypertension also contributes to an increase in the rate of replication and the permeability of the endothelial cells, leading to intimal edema. In chronic hypertension prominent intimal thickening has also been demonstrated. Any thickening of endothelium can decrease the flow of nutrients to intima and inner media by impairing transintimal diffusion. Theoretically this situation can lead to deterioration of the elastic lamina

and collagen architecture of the arterial wall. According to Ferguson GG injury to underlying elastic lamina by hemodynamic forces is the initial pathophysiological alteration. Because arterial bifurcations are the site of greatest shear forces against the arterial wall such injuries usually occur at these sites.

2. **Occlusion of vasavasora:** The existence of vasavasorum of intracranial vasculature has long been debated. Connolly demonstrated the existence of vasavasorum in intracranial arteries in human cadavers. The tunica adventitia and outer media of the intracranial blood vessels are thought to be supplied by vasavasorum whereas the intima and inner media are nourished by diffusion from the lumen. The middle zone is most susceptible to hypoxia. It has been suggested that occlusion of vasavasorum caused by hypertension could play an important role in ischemia and necrosis of the vessel wall and cause damage leading to aneurysm formation.
3. **Disturbance of elastin and collagen synthesis:** Hypertension causes damage to elastin and also increases the biosynthesis of collagen in cerebral arteries. Consequently the normal elastin collagen ratio is disturbed, and elastin is gradually lost. In chronic hypertension, the elastin is replaced by collagen. Thus hypertension directly affects the metabolism of connective tissue in the cerebral arteries. These changes may be irreversible even after treatment of hypertension[12].

SMOKING: Cigarette smoking at any time may promote enlargement of intracranial aneurysms by mechanisms that are not yet well understood. It has been postulated that smoking promotes degradation of elastin in the blood vessels walls, making the walls susceptible to dilatation under load produced by the blood pressure at anatomical sites of maximal turbulence[13]. Smoking appears to be the only modifiable risk factor for formation of aneurysm.

INFLAMATION:

Handle and Blumenthal proposed an inflammatory factor in the pathogenesis of intracranial aneurysms. It has been described that the inflammation results in the formation of the gaps in the elastic lamina. In the first stage the inflammation involves all the layers of the wall, including the elastic lamina. Resolving inflammation leaves gaps in the elastic layers and the muscular layer is replaced by fibrous tissue, thus setting the stage for aneurysm formation. However inflammation is uncommon and this hypothesis has not attracted much support.

MYCOTIC ANEURYSMS:

In 1885 Osler introduced the word "Mycotic" to describe the lesion in the aortic arch in patients with endocarditis. Eppinger 1887 termed "Mycotic embolic aneurysm". Bohmfalk et al introduced the term "Bacterial intracranial aneurysm". The common organisms involved are *staphylococcus aureus*, *staphylococcus albus* and *streptococcus viridans*. The fungi which that known to cause cerebral aneurysms include *Aspergillus*, *mucor*, *pencillium*, *candida*, *coccidiodes* The incidence of mycotic aneurysm has been reported as being 2.6% of all intracranial aneurysms. The actual mechanism involved in the spread of infection and the formation of mycotic aneurysm are still controversial. Studies suggest that

infective organisms seep into Virchow Robin spaces, migrate distally and affect the vessel wall transmurally from adventitia to intima, lead to vessel wall weakening and formation of aneurysm[15]. Various other modes in pathogenesis described are

1. Direct extension from the lumen through the wall (intima to adventitia).
2. Through the vasovasorum
4. By direct extension of an infective focus around an artery.

TRAUMATIC ANEURYSMS:

Traumatic aneurysms account for 0.5% of all cerebral aneurysms found, these do not occur at the bifurcation of arteries. Burton et al divided these into

1. *Direct penetrating injuries and iatrogenic injuries:* A vessel may be injured when it lies in the path of a penetrating object or in a surgical field. These aneurysms are irregular in contour and generally without a discrete neck.
2. *Indirect closed head injuries:* Following closed head injury, aneurysms arise as a consequence of dynamic forces, which disrupt the walls of an artery.

OTHER CAUSES: Other causes described for saccular aneurysm include neoplastic, disorders of blood vessels and radiation induced.

FUSIFORM ANEURYSMS:

The various causes for the formation of fusiform aneurysms includes atherosclerosis, genetic including Marfan's syndrome and Pseudoxanthoma elasticum, infectious casues including syphilis and fungal infections, disorders of blood vessels including gaint cell arteritis , congenital disorders like coarctation of aorta and those due to radiation

Results and Analysis

Results and analysis

Clinical data

There were 57 patients whose aneurysms were excised during the period of Jan 1999 - Dec 2000. The age range was 17 - 65 years (mostly in 5th and 6th decades) with 33 males and 24 females (Table I). Chronic smoking was seen in 26 patients, hypertension in 19 patients, and diabetes mellitus in 3 patients (Table II). Estimation of total serum cholesterol was done in 23 patients of whom only 5 patients had a raised value. Serum HDL-cholesterol level, done in 23 patients, was low in 14 patients (Table II). Nineteen cases belonged to the highest income category and 38 cases belonged to the lower income categories (of our hospital) at admission. Fifty-two patients had presented with subarachnoid hemorrhage and 5 without subarachnoid bleed. Those without subarachnoid bleed had presented with, normal pressure hydrocephalus syndrome, third nerve palsy, seizures, chronic headache and with progressive loss of vision. 1 patient was in *GCS -13*, 8 were in *GCS -14*, 48 were in *GCS-15*, and 9 were in *WFNS 2* and 48 were in *WFNS 1*. Six patients had papilloedema, 4 had third nerve deficits, 5 had sixth nerve deficit and another 5 had seventh nerve deficit, 13 had limb weakness, 3 had dysphasia, and 9 had neck stiffness. All the pts were operated following DSA except one who was operated based on CT Angiogram alone (Left DACA aneurysm). All the patients underwent surgery with clipping of the aneurysms and excision of the sac. Aneurysms involved both anterior (52 cases) and posterior (5 cases) circulation. Where possible, in cases of fusiform aneurysms, the adjoining segment of the affected vessel

Table No: I

Age distribution and mucoid changes

Age	FAM	FANM	TAM	TANM
11-20	1	2	0	0
21-30	1	1	0	1
31-40	4	0	1	1
41-50	8	10	5	1
51-60	6	4	4	0
61-70	2	2	3	0
Total	22	19	13	3

FAM: False aneurysm with mucoid change
FANM: False aneurysm without mucoid change
TAM: True aneurysm with mucoid change
TAM: True aneurysm without mucoid change

was also excised. Apart from vasospasm in 7 patients there were no other abnormal angiographic findings. Fifty-four aneurysms were saccular and three were fusiform (2 were vertebral artery dissecting aneurysms and one was M2 segment aneurysm). Thirty-nine of the patients were normal on follow up, 7 had significant residual neurological deficits, 5 patients had expired and 6 were lost to follow-up.

Histopathology:

Histologically the biopsy samples were classified as: true and false aneurysms (Table. II). The histomorphological features are shown in Fig.1 and Fig.2. In 7 of the false aneurysm cases, the specimen consisted of extravasated blood clot only, surrounded at places by a thin rim of adventitial fibrous connective tissue. Amongst 50 cases with an identifiable aneurysm sac, there were 16 true aneurysms and 34 false aneurysms. True aneurysms were identified by the presence of intima, internal elastic lamina and medial elements in the wall, often with an abrupt or gradual transition to false aneurysm structure, suggestive of focal rupture of the aneurysm sac. The internal elastic lamina of true aneurysms and of the proximal artery stump where available, showed varying degenerative changes. It appeared thick and beaded or thin attenuated and reduplicated, with focal fragmentation. In false aneurysms, organizing blood was contained by a fibrous wall, lacking internal elastic lamina and media, and lined by a layer of thin or thick exuberant granulation tissue. In 13 true aneurysms and 22 false aneurysms (Table. I), the wall had a varying thickness with large pools of acid mucopolysaccharide material. The mucoid material was seen between hyperplastic spindle-shaped and stellate myofibroblasts and in true aneurysms, in the intima

Figure 1.

A, B, C, D. Parent artery (A,B,C) and vasavasorum (D) have thick intima with vacuoles of mucoid material in intima and media between hyperplastic smooth muscles cells. The internal elastic lamina (in A,B,C) shows reduplication, focal thickening and fragmentation. (A: HE*240, B: Toluidine blue*240, C: Verhoeff van Gieson*240, D: HE*96).

E, F. True aneurysm with organizing mural thrombus and a thick lining that contains pale-staining mucoid material between myofibroblasts. There is thinning of the fundus of the sac wall with focal rupture and transition to false aneurysm structure. (E: HE*24, F: Verhoeff van Gieson*24).

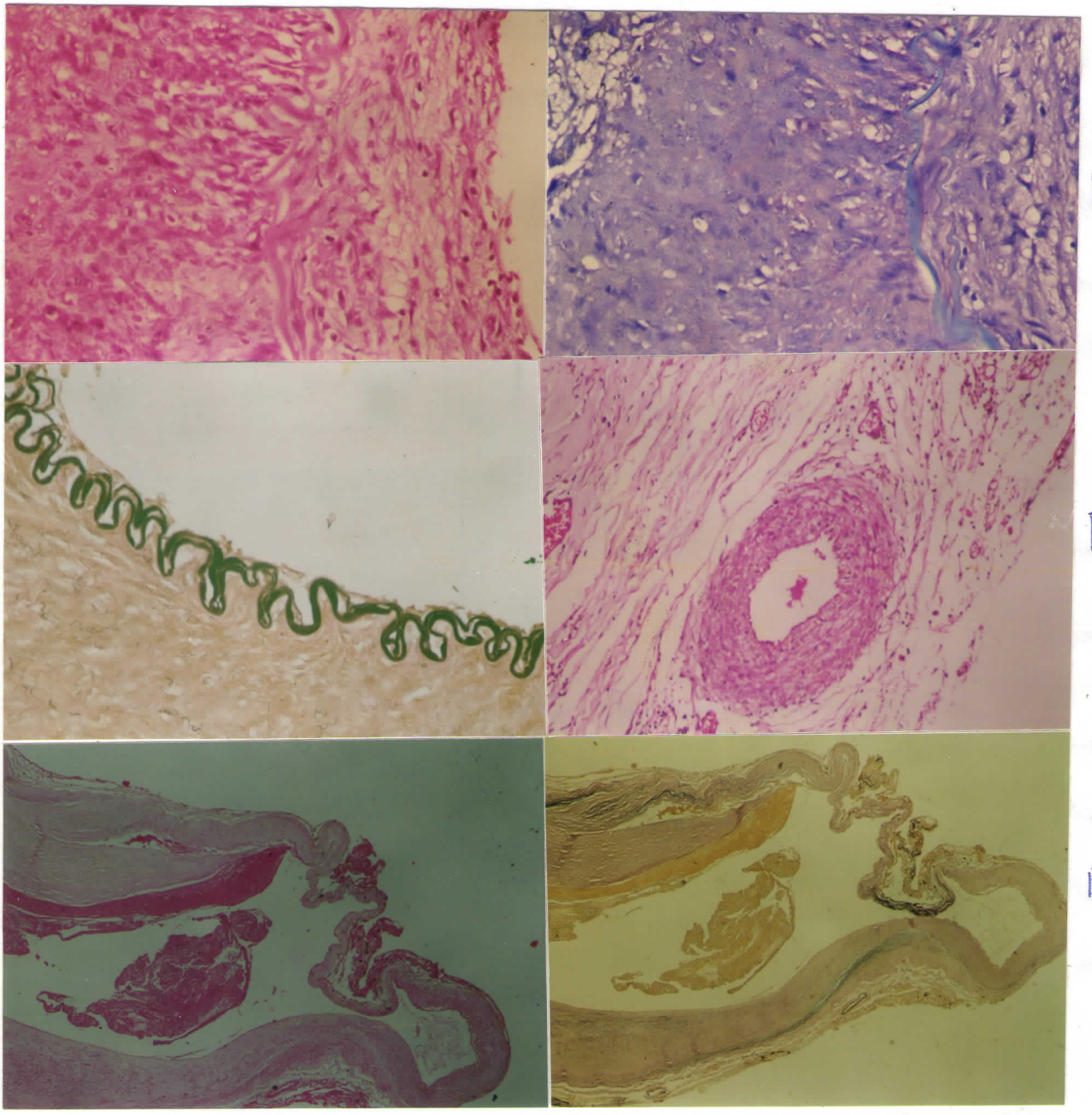
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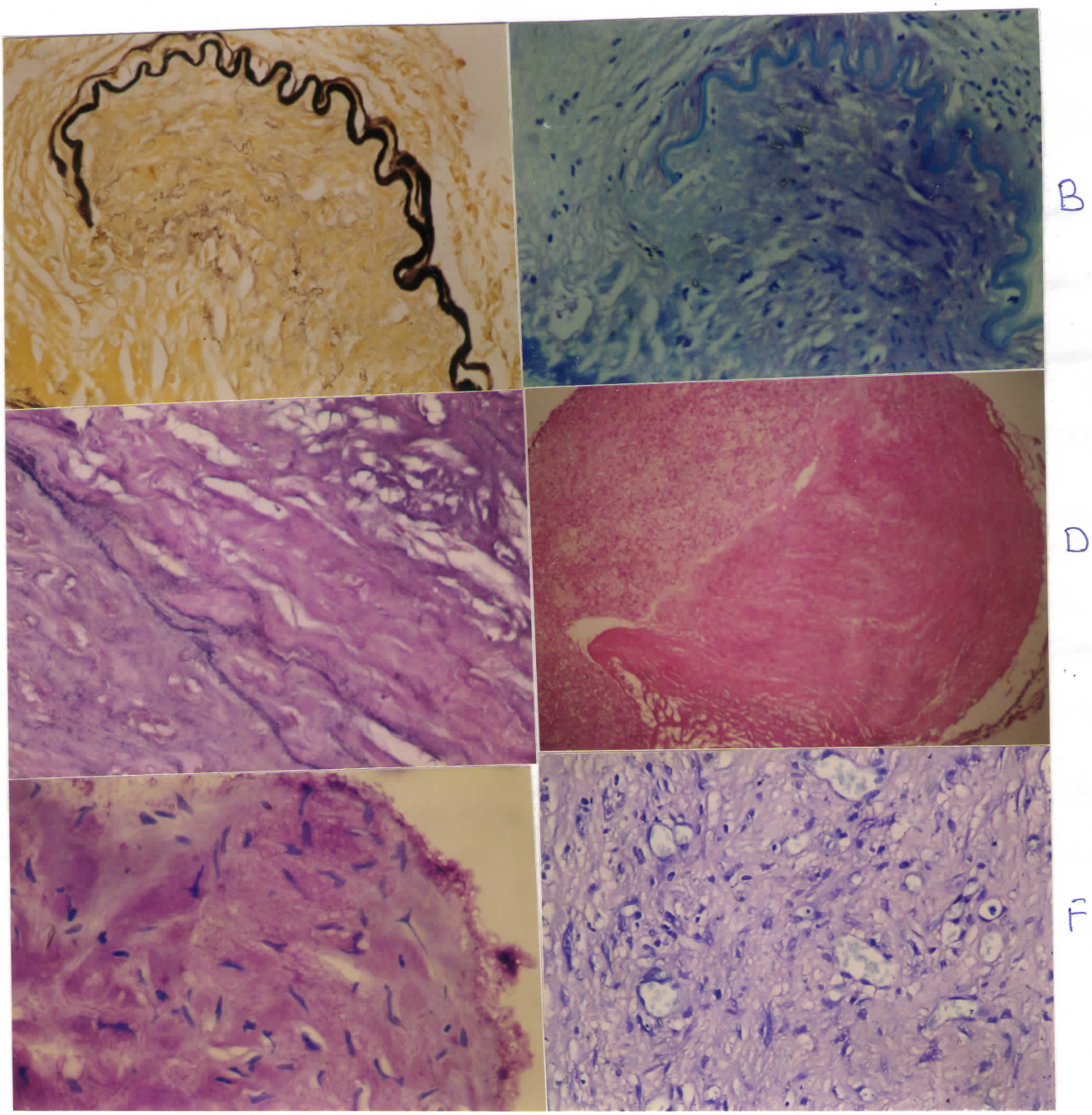
Figure 2.

A, B. True aneurysm with reduplicated and beaded thick internal elastic lamina shows organizing thrombus at point of rupture. Deposits of magenta coloured mucoid material are seen in intima and media around dystrophic internal elastic lamina between hyperplastic cellular elements, adjoining the site of rupture. (A: Verheoff van Gieson*240, B: Toluidine blue*240).

C. True aneurysm wall shows remnant strands of internal elastic lamina at base of a large myxomatous nodule. (C: Verhoeff van Geison*385).

D, E. True aneurysm with rupture shows nodular mass of organizing thrombus contained by thin fibrocollagenous wall and a cap of myxomatous tissue, bulging into the aneurysm lumen. The myxomatous nodule (E) contains large pools of magenta coloured acid mucopolysaccharide material and stellate, elongated, hyperplastic myofibroblasts. The mucoid material is seen in surface layer of endothelial cells also. (D: HE*40, E:Toluidine blue*385).

F. Granulation tissue in an organizing blood clot shows numerous thin-walled capillaries, fibroblasts and minimal amounts of extracellular mucoid material, lining a fibrohyaline aneurysm wall. (F: Toluidine blue*96).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and between medial smooth muscle cells also. In some of the cases, this appeared as mucoid intimal plaques or nodules of myxomatous tissue bulging into the lumen of the aneurysm. The proximal artery stump and vasa vasora in some of these cases also showed mucoid degenerative changes in the intima and media. Focal spotty calcification and hemosiderin deposits were noticed in the aneurysm wall in some cases. There was no evidence of inflammation and atherosclerosis in any of the sections of the proximal artery, nor any lipid deposits (atheromatosis) in the aneurysm sacs.

Clinico-pathological correlation:

Mucoid changes was seen in 5th and 6th decades. There were 20 males and 15 females with mucoid changes. Multiple aneurysms with mucoid changes were common in females (4 cases) and MCA aneurysms were more common in males (8 cases). Amongst the 35 cases with mucoid changes, 18 were chronic smokers, 15 were hypertensive, 2 were diabetics (Table II). Of the 23 patients in whom lipid profiles were investigated, only 2 patients had a raised serum cholesterol level and 9 had a low serum HDL-cholesterol level. Ten of the 19 patients in "D" group (highest income category of our hospital) had mucoid changes; 12 of the 38 in the lower income groups had mucoid changes. Thirteen of the 16 true aneurysm cases and twenty two of the 34 false aneurysm cases showed mucoid degenerative changes and approximately half of the true and false aneurysm cases were associated with risk factors like hypertension and smoking (Table II).

Table II

Sex incidence and risk factors in relation with mucoid changes

	Total(57)	**Mucoid Changes(35)**	**FAM (22)[¶]**	**TAM (13) [§]**
Females	24	15	10	5
Males	33	20	12	8
Hypertension	19	15	9	6
Chronic smoking	26	18	11	7
Diabetes	3	2	1	1
Serum Cholesterol	5	2	1	1
HDL	14	9	2	1

[¶]FAM:- False aneurysm with mucoid changes. Total of 22 pts

[§]TAM:- True aneurysm with mucoid changes. Total of 13 pts

Discussion

Discussion

Aneurysmal vascular disease at various sites, including cerebral vasculature, was often encountered at SCTIMST, Trivandrum. In the last decade there was a considerable increase in the number of cerebral aneurysm cases operated upon at this Institute. The number increased from 88 cases in the year 1990 to 136 in the year 2000. Cases of mycotic aneurysm, mostly iatrogenic, following lumbar puncture at peripheral hospitals, were referred to this Institute and earlier reported[1,2,3]. Besides these, in a large number of cases, the exact nature and cause for the aneurysms were not clear. No infective organisms were demonstrated histologically, nor did the patients have any associated inherited forms of connective tissue disorders. There were no cases with tumour embolism. A clinico-pathological study was therefore initiated.

The present study, carried out on 57 consecutive cases over a period of 2 years, focuses our attention on distinct mucoid degenerative lesions in a significant number of cases and their association with known risk factors like hypertension and smoking. As per the available literature aneurysmal rupture is more common in 6th and 7th decades of life[8]. In our study group it was seen in a decade young age, the maximum incidence was in 5th and 6th decades. There is a clear female preponderance (1.6:1) reported in literature[9], however in our study, males dominated( ). Hypertension was reported in about 16% to 43.5% of patients with aneurysmal subarachnoid hemorrhage[10,11,12]. We found hypertension in 33.33 % (19 of 57 cases). Smoking, another important risk factor for cerebral aneurysms[13] was seen in 45.6 % (26) of our cases. Although reported occasionally[14], atherosclerosis is not

considered an important risk factor for cerebral aneurysms[15]. Among the cases which presented without subarachnoid bleed 4 had mucoid changes, 3 of them having true aneurysm and one having false aneurysm. The other one without mucoid change was a false aneurysm

The etiopathogenesis of cerebral aneurysms is uncertain and the cause of subsequent rupture is not evident in all cases[16]. There is controversy whether aneurysms are congenital or acquired in nature and to what extent environmental risk factors are involved in their pathogenesis. The congenital theory hypothesizes a weakness in the artery wall due to maldevelopment[17]. Support for a congenital origin comes from the frequency of multiple aneurysms, familial occurrence of aneurysms and association of systemic inherited diseases of vascular connective tissue, such as Marfan's syndrome, Ehlers-Danlos syndrome and inherited forms of dyscollagenosis and polycystic kidney[18,19]. Alternately, the degenerative theory suggests an acquired defect in the vessel wall[20,21,22,23,24,25,26,27,28]. This theory is supported by the increased frequency of aneurysms with age, hypertension, smoking and arteriosclerosis[25]. The present consensus is that atherosclerosis does not lead directly to formation of aneurysms[15,25]. Combinations of maldevelopment and degeneration may also exist. It is known that cerebral arteries differ from extra-cranial vessels in having a thin or absent external elastic lamina. Structural integrity is provided by the internal elastic lamina, the cellular elements dispersed in the extracellular ground substance and fibrillary proteins in the matrix of the intima and media. Any alterations or damage in these vessel wall components, especially the internal elastic lamina and media, along with local hemodynamic factors can lead to the development of aneurysms[28,29,30]. The effects of associated risk

factors, particularly hypertension and smoking, may be mediated through damage to the internal elastic lamina[15,25].

A review of literature revealed the occurrence of cerebral aneurysms (saccular and dissecting types) with mucoid degeneration, in other parts of the world also, but these were only sporadic reports of single or small number of cases[29,27,31]. and therefore not directly comparable with our cases. Various authors used different terminologies such as mucoid vasculopathy, cystic medial necrosis[32,33], intimal fibro elastic thickening[34], medial mucoid degeneration[35], segmental mediolytic arteriopathy[36], myxoid degeneration[27], and mediolytic arteriopathy[37], to describe the nature of the lesions in cerebral and extra cerebral cervical vasculature. In all these reports, the common finding was deposition of mucoid material in the intima and media with fragmentation of internal elastic lamina causing weakening of the vessel wall. Generalized involvement of extra cranial vessels in addition to cerebral vessels has been reported by some[31,37]. Associated risk factors like hypertension and smoking resulted in further weakening of the wall leading to aneurysm formation, dissection and even rupture[27].

Mucoid vasculopathy is a non-atherosclerotic, non-inflammatory disorder, with generalized deposition of abnormal acid mucopolysaccharides in the walls of blood vessels, accompanied by dystrophic changes in elastin and collagen[5,6,7]. Besides stenotic lesions, the condition was responsible for aneurysms at various sites, such as aorta, pulmonary artery and carotid artery[38,39,40,41,42]. A monkey model established the role of nutritional imbalance with low-protein high starch diets in its aetiology[43]. Mucoid vasculopathy is similar to mucoid arteriopathy and aortopathy described from Uganda[44,45] ,and to intimo-medial

mucoid degeneration described from South Africa [46,47,48] where similar diets as consumed in Kerala, may be responsible for mucoid degenerative vascular disease[49].

This study has shown the presence of mucoid degeneration and dystrophic internal elastic lamina in the aneurysms of a significant number of patients. It is well known that structural gaps in internal elastic lamina are responsible for development of cerebral aneurysms at bifurcation points[20]. Such gaps aggravated by acquired degenerative changes in elastic laminae may predispose arteries to aneurysmal dilatation at bifurcation and non-bifurcation sites in our cases. It can be postulated that mucoid degeneration and dystrophic changes in internal elastic lamina in blood vessels are brought about by an acquired disorder of mucopolysaccharide and protein metabolism due to an exposure to a low protein and high carbohydrate diet for many years. This mucoid and elastic tissue degeneration or mucoid arteriosclerotic vasculopathy, weakens the vessel wall and when combined with risk factors like hypertension and smoking, may lead to the formation of aneurysms in the 5th and the 6th decades of life. The presence of such histopathological lesions in the parent vessel and in the walls of true and false aneurysms appears to reflect the underlying diet induced metabolic disorder and tendency to lay down excessive amounts of myxomatous tissue during organization of a thrombus or extravasated blood. Estimation of serum mucopolysaccharides was done in a few of our patients and was found to be elevated This test may be an important marker for the underlying metabolic disorder.

This clinicopathological study initiated at SCTIMST highlights the necessity of carrying out detailed investigations including histopathological studies and serological markers, to diagnose and treat the underlying vascular disorder. The studies will help to formulate primary and secondary preventive measures for cerebral aneurysms.

Conclusions

Conclusions

This study has shown the presence of mucoid degeneration in the aneurysms in a significant number of patients, besides conventional risk factors such as hypertension and smoking in some. This study needs to be further elaborated with detailed investigations including serum mucopolysaccharide levels and lipid profiles, and delineation of dietary and other risk factors that could have a role in the etiopathogenesis of cerebral aneurysms. Such studies may provide a basis for development of definite animal models for cerebral aneurysms in future.

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