# SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY
## Thiruvananthapuram- 695011

**THESIS FOR THE DEGREE OF MCh NEUROSURGERY**



**Name:** **Dr. S Bhaskar**

**Month and Year of Submission:** **April 2005**

# RISK FACTORS FOR CEREBRAL ANEURYSMS: A CLINICOPATHOLOGICAL STUDY

**THESIS FOR THE DEGREE OF MCh NEUROSURGERY**
**SCTIMST, THIRUVANANTHAPURAM**

**DR. S. BHASKAR**
**APRIL 2005**

# *ACKNOWLEDGEMENT*

The submission of this thesis brings to culmination three years of fruitful and productive association with Dr. R.N.Bhattacharya, Professor and Head of the department of Neurosurgery under whose expert guidance and kind cooperation I was able to complete the work to the best of my satisfaction. He will be a source of constant inspiration to me.

I would like to thank Dr. S.Sandhyamani, Professor, Department of Pathology who guided and helped me immensely and made the completion of this thesis possible.

I would also like to thank Dr. S.Nair, Professor of Neurosurgery for his invaluable advice and guidance during the course of the study.

I would specially like to thank Dr. B.J.Rajesh for his guidance and encouragement without which this work would not have been possible.

The critical remarks and suggestions of Dr. BRM Rao and Dr. Girish Menon have been invaluable.

I am grateful to Dr.K.Mohandas, Director, for institutional help, Dr.V.V.Radhakrishnan, Professor of Pathology for his comments on histology of some of the cases in the study, and to the technical staff of the department of pathology.

I would also like to acknowledge the help that my various colleagues, senior and junior extended to me during the course of the study. A special thanks to Dr. Easwer, Dr. Muthu Retnam, Dr. Mathew, Dr. Mukund, Dr.Raghavan and Dr. Harshad.

I would like to thank Ms. Priyanjana Prabhakar for carrying out the serum glycosaminoglycan estimation, Mr. N.S. Radhakrishnan and Mr. Liji for technical assistance.

I want to acknowledge the kind co-operation extended to me by the various staff, be it the nursing staff in the wards/ICU and in the neurosurgery operation theatre.

Last but not the least, I would like to thank all my patients who underwent the relevant investigations, treatment and reported for follow up as and when asked to do so.

S. Bhaskar

Dr.S.Bhaskar

# *CERTIFICATE*

This is to certify that this thesis entitled "Risk factors for cerebral aneurysms: A clinicopathological study" is a bonafide work of Dr. S.Bhaskar and was conducted in the Departments of Neurosurgery and Pathology, SCTIMST, Thivananthapuram under our guidance and supervision.


DR.S.SANDHYAMANI
Professor
Department of Pathology
SCTIMST, Thiruvananthapuram

DR. R.N.BHATTACHARYA
Professor and Head
Department of Neurosurgery
SCTIMST, Thiruvananthapuram

# *CONTENTS*

# INTRODUCTION

# Introduction

Cerebral aneurysms and the resultant subarachnoid haemorrhage cause significant mortality and morbidity. The outcome after subarachnoid hemorrhage due to aneurysmal rupture is still grim; mortality rates range from 40-50%, severe disability in 10-20% patients and only 40% reach independent status.[1,2] So "prevention is better than cure" would apply very well in case of cerebral aneurysms, if only the causative factors were known. Unfortunately only a few etiological factors have been established for the intracranial aneurysms. In a previous clinicopathological study from this institute, surgically excised cerebral aneurysms specimens' revealed mucoid vasculopathic changes.[3] Mucoid vasculopathy is a non-atherosclerotic vascular disorder observed at this institute by Sandhyamani[4] in a significant number of patients amongst our population. The disorder causes stenotic and aneurysmal vascular disease at various sites.[5] A primate model established the role of nutritional imbalance with low protein and high starch diets, in the etiology of this condition.[6,7]

As the earlier study revealed mucoid vasculopathic changes in a significant number of cases, this study was undertaken to establish the various risk factors associated with these changes in cerebral aneurysms

# AIMS & OBJECTIVES

# Aims and Objectives

To study the various risk factors associated with cerebral aneurysms in patients reporting to this institute.

1. To assess lipid profiles of these patients.

2. To estimate serum levels of total glycosaminoglycans (GAG).

3. To correlate these biochemical parameters with clinical features and with histopathological findings of biopsies obtained at surgery.

# REVIEW of LITERATURE

# Review of Literature

The reasons for the development and rupture of cerebral aneurysms are not clear, but possible etiological factors considered are either congenital, inherited or acquired defects.[10] The propensity for humans to develop cerebral aneurysms as compared to lower animals, is attributed to longevity and higher incidence of risk factors like hypertension, smoking etc, which weaken the wall of the blood vessel. The preponderance for cerebral vessels to develop aneurysms is due to is due to architectural peculiarities, namely thin media, thin adventitia and an absent external elastic lamina.[13] Structural integrity of blood vessels 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.

Several factors have been implicated in increasing the risk of genesis of aneurysm, including hypertension, atherosclerosis, female sex, aging, smoking, use of oral contraceptives, alcohol consumption, collagen Type III deficiency, asymmetry in circle of Willis, cerebral AVMs, viral infections, pituitary tumors, and certain HLA associated factors. Among these smoking, alcohol consumption and to lesser extent hypertension seem to be the modifiable risk factors for aneurysm formation.[2] Aneurysmal rupture is extremely uncommon in the first decade.[10] The incidence gradually increases for each decade and peaks in the 6$^{th}$ decade. The aneurysm rupture rate increases with age but this risk declines in extreme of old age. Cerebral aneurysms are found more frequently in women than men. Hormonal factors like, the lack of protective effect of estrogen has been implicated.[10] A similar mechanism might be involved in the formation of multiple aneurysms in post menopausal women.

**Congenital factors:** The congenital theory evolved from concepts like defects in cerebral arteries, which could not be proven. The association of aneurysms with polycystic kidney disease, coarctation of aorta was assumed to be due to congenital factors and not the degenerative changes that are very marked in these conditions. Gull[12] in 1859 proposed that a berry aneurysm was a simple pouch with the sac wall transparent and normal in appearance as the parent vessel, giving the impression that it was due to a preexisting deformity and considered it as congenital in origin.

Aneurysms arise from the bifurcations and adjacent walls of the large cerebral arteries that have high blood flow rates. Increased flow at these sites could be due to aplasia of contra-lateral vessels and congenital variations in the circle of Willis. Hemodynamic factors like uneven pulsatile pressure head distribution at the apex of the arterial branching causes local degeneration of internal elastic lamina.[13] The congenital theory of origin of aneurysm was challenged due to the following reasons[12]

1. The incidence in the first 2 decades of life is rare.

2. It was assumed that medial raphe was a congenital physical defect in the wall, which is not the case.

3. The association with congenital abnormalities and variations in the circle of Willis and aneurysms was not statistically proven.

4. Changes noted in the aneurysm biopsies were thought to be due to atherosclerosis (which has also been subsequently disproved).

5. Structural lesions like media and elastica defects and preaneurysmal lesions like infundibula were thought to predispose to the wall weakening (disproved).

**Inherited Factors:** The presence of a genetic predisposition manifesting as a defect in the vascular composition can lead to formation of an aneurysm. It is evidenced by aneurysms being more common in certain families (approximately 10% of cases) or sometimes its occurrence with diseases like Ehlers-Danlos syndrome.[14]

**Acquired Factors:** Aneurysms seem to be acquired degenerative lesions that develop as a result of hemodynamic stress. Several clinical observations support this theory, [14]

1. Aneurysms develop at arterial bifurcation where stress is maximal.

2. Increased incidence with age (Rare in children)

3. Aneurysms are found on high flow feeders of AVMs (arteriovenous malformation).

4. Hypertension seems to be general risk factor for aneurysm development.

5. Some authors attribute aneurysms formation to a congenital defect in the arterial wall in association with degenerative change. Carmichael mistook areas of mural thinning

for the medial defects or raphes described by Forbus[15]. Experiments demonstrated that the mural thinning could be produced by hemodynamic means in the absence of specific connective tissue disease, thus substantiating a degenerative etiology. Stebhens[12] contended that the three most likely methods of producing cerebral aneurysms were by experimental hypertension, coarctation of aorta, and cerebral arteriovenous fistula.

6. Incidence of unruptured aneurysms in autopsies in adults is only 5%
7. Other established causes include trauma, infections, radiation induced and neoplasms. Diseases like systemic lupus erythematosus and Moyamoya disease may also cause aneurysms.[10]

**Cigarette Smoking:** Long-term smoking can cause formation of aneurysm by weakening of the wall of the cerebral arteries. Many studies have shown cigarette smoking to increase the risk of SAH.[16,17] In North America and Europe the prevalence of smoking in patients who suffer SAH ranges from 45-75%, whereas in the general population it is 20-35%. Pathophysiological mechanism for the formation of cerebral aneurysm due to smoking:

- Increased elastase activity and decreased anti-trypsin activity can lead to aneurysm formation or SAH. Topical application of elastase (but neither collagenase or papavarine) experimentally to the arterial wall causes saccular aneurysm formation, growth and even rupture.[18]

- Smoking enhances the formation of atheroma by altering platelet function and inhibiting enzymes involved in the vessel wall repair system. This damage might make vessels more susceptible to dilatation in response to blood pressure at points of maximum turbulence.

- Smoking promotes atherosclerosis in the carotid arteries that could affect hemodynamic stress in the circle of Willis.

- Smoking elevates blood pressure albeit transiently.

Smoking seems to be the most important modifiable risk factor for SAH since 38-48% of SAH can be attributed to current smoking.[16]

**Hypertension:** Vessel wall damage caused by stress due to a hypertensive circulation, especially that found at the vascular bifurcation and other branching sites, may cause the initial wall weakness that predisposes to aneurysm formation.[19,20] The mechanisms by which hypertension increases the risks of aneurysm formation are- endothelial injury, occlusion of vasa vasora and disturbance of the elastin and collagen synthesis.[20] Animal experiments have shown that saccular aneurysms very similar to the ones seen in humans can be produced by experimentally induced hypertension. But the fact many patients with aneurysms do not have

hypertension and the prevalence of hypertension indicates that other factors are also essential for aneurysm formation. Hypertension may be a significant risk factor for impaired outcome after SAH. High systolic BP values after aneurysm rupture predict independently of other prognostic factors, death, poor outcome, and possibly occurrence of early rebleed. Chronic hypertension induces hypertrophy of the arteriolar smooth muscle cells and shifts the cerebral auto regulation curve to the right. This and the narrowing of the arteries may render these patients more vulnerable to cerebral ischaemia during episodes of relative hypotension.

The consensus now is atherosclerosis does not lead directly to aneurysmal formation.[10]

The factors correlating with the increased incidence of multiple intracranial aneurysms are hypertension, smoking, a family history of cerebrovascular diseases, and the postmenopausal state in female patients.[21]

In a earlier study done at this institute aneurysm biopsy revealed mucoid deposits between hyperplastic cellular elements in the true and false aneurysm wall and/or parent artery or vasa vasora.[3] The changes were associated with dystrophic changes in the internal elastic lamina. Mucoid degeneration has been reported in cerebral aneurysms in other regions of the world but those have been in a few cases only. It has been also been reported in extra cranial vessels (cervical, brachial).[22,23,24,25,26] The various synonyms used are cystic medial necrosis,[27,28] intimal fibro elastic thickening,[29] medial mucoid degeneration,[30] segmental mediolytic arteriopathy,[31] and myxoid degeneration[32] and mediolytic arteriopathy.[33] The findings in all these were deposition of mucoid material in the intima and media with fragmentation of the internal elastic lamina causing weakening of the vessel wall. Mucoid vasculopathy is the result of consumption of a diet low in protein and high in starch content

that is common in this part of the country; it might be the cause for mucoid vasculopathy in cerebral vessels and aneurysm formation.[4] Associated risk factors (hypertension, smoking) further weakened the wall causing rupture in many cases.

**Pathophysiological mechanism for aneurysm formation:**

One of the hypotheses in the formation of an aneurysm is the remodeling of the extracellular matrix (ECM) of the vessel wall.[34] The ECM is a dynamic network of proteins and proteoglycans that are essential for both structural and functional processes. Collagen and elastin embedded in proteoglycans and glycoproteins are the main elements in the arterial wall determining its tensile strength. Changes in the elastin-collagen ratio or in the proteoglycan composition will alter the mechanical properties of the arterial wall. The same components are also present in the aneurysm wall, but their content and structure are changed. Based on these observations it appears that this might be a common pathway in the mechanism of cerebral aneurysm formation.

# MATERIALS & METHODS

# Materials and Methods

The study group included 160 consecutive patients with cerebral aneurysms managed at our hospital during the 2-year time period, January 2003 through December 2004. Of the 160 patients 152 patients underwent surgery for aneurysms. The clinical parameters included were age, sex, economic status, WFNS grade at the time of admission, risk factors, radiological data, lipid profiles, and serum levels of glycosaminoglycans (GAG). Serum lipid profiles were routinely estimated in 145 patients on admission, using standard kits (Dade Behring). Serum GAG was estimated in 83 patient and was isolated from 0.5 ml of serum by a simple micro method standardized in our lab (Priyanjana et al, under publication), which is a modification of Niebes and Schiffler's[51] method. Estimation of GAG was done by Blumenkrantz and Asboe- Hansen[52] method using a spectrophotometer (SHIMADZU, UV-2101PC). Using this method, serum GAG levels in healthy young adults (18-25 years) with normal BMI (body mass index) amongst voluntary blood donors, established normal range quoted in this study (males: up to 1.68 mg/dl and females: up to 1.13 mg/dl).

Fifty-three of the aneurysms could be excised for histopathological analysis. The aneurysm sacs were fixed in buffered formalin processed through graded alcohol and embedded in paraffin wax. 5μ thick sections were examined, using haematoxylin and eosin, Verhoeff van Gieson's and Toluidine blue staining techniques. Histopathological findings were correlated with other clinical and biochemical parameters.

# RESULTS & ANALYSIS

# Results and Analysis

Among a total number of 160 patients with SAH due to aneurysmal bleed included in the study, the ratio of females to males was 0.8:1.0 (males-87 and females-73). The age range was 14 – 85 years (mean- 36yrs). Maximum numbers of patients were in the age group of 41-60 years (99/160). The age distribution among the patients with aneurysms is shown in Table 1. One hundred and forty four aneurysms were in the anterior circulation and 16 in the posterior circulation. The location of aneurysms is as shown in Table-2. Multiple aneurysms were present in 15 patients, 13 had two and 2 had three aneurysms each. Anterior communicating artery and middle cerebral artery aneurysms in 08, anterior communicating artery and internal cerebral artery in 01, middle cerebral artery and internal cerebral artery in 03, middle cerebral artery and basilar artery in 01. The profile of the patients with multiple aneurysms is as shown in Table-3. At admission, 87 patients were in the higher income group as per our hospital criteria and 73 in the lower groups. 147 patients presented with headache, 4 had seizures and 6 patients had third nerve deficits preoperatively. GCS at admission was 15 (128), 14(15), 13(03), 9-12(10) and 3-8(04). Accordingly WFNS grade at admission was Grade 1 and 2 in 142 cases and Grades 3 to 5 in 18 cases. Focal limb deficits were noted in 12 patients at the time of admission. 15 patients had diabetes mellitus and pre-existing hypertension was present in 59 patients. 11 patients had both diabetes and hypertension. 57 patients were smokers and 27 consumed alcohol. 02 patients had preexisting renal diseases with hypertension. Lipid profiles were available in 145 patients. Total serum cholesterol was elevated in 29 (>240mg/dl), borderline in 51(200-240mg/dl) and normal in 65(<200mg/dl) patients. Triglyceride (TG) levels were high (>200mg/dl) in 24, borderline (150-200mg/dl) in

22 and normal (<150mg/dl) in 99 patients. High density lipoprotein (HDL) was low (<39mg/dl) in 19, borderline (40-44mg/dl) in 33 and normal (>45mg/dl) in 93 patients. The percentage of patients with normal and deranged lipid profiles is shown in Table-4. Fisher grades on preoperative CT were Grade1 (36), 2(26), 3(63), and 4(35). 152 patients underwent surgical clipping of the aneurysm. 08 patients were not operated (refusal of consent for surgery, death due to rebleed). 132 of these operated patients were doing well on follow up, 03 patients were lost on follow up. 05 patients had deteriorated in the immediate post op period and on follow up were recovering. 20 patients died out of which 03 died in the preoperative period due to rebleed and rest were postoperative mortalities (vasospasm, septicaemia, pulmonary embolus).

Biopsy was obtained in 53 of the patients. Histopathological features are shown in Figure-1 and analysis is tabulated in Table-5. The aneurysms were classified as true and false aneurysms, with and without mucoid changes or blood only. True aneurysms were those where intima, internal elastic lamina and medial elements were identified. Transition either abrupt or gradual to a false aneurysm indicated a focal rupture. The internal elastic lamina in the sac, and the proximal artery stump wherever available were studied and various degenerative changes were observed. It was thickened and beaded or thin attenuated and reduplicated, with focal fragmentation. False aneurysms consisted of extravasated blood lined by a thin layer of adventitial fibrous connective tissue only, lacking internal elastic lamina and media. Analysis of the biopsy samples showed 21 true aneurysms and 15 false aneurysms with mucoid deposition in the wall; 08 specimens with myxomatous plaques and 02 with large pools of extruded mucin within the blood. The vasa vasora in 4 showed mucoid degenerative changes. The proximal stump showed acute dissection in one of the specimens.

mucoid change in the biopsies (06 with true aneurysms and 07 with false aneurysms). 01 patient had a false aneurysm without mucoid change and one biopsy revealed only blood. The levels of GAG in these patients was elevated in 11 of the 13 patients whose biopsies revealed mucoid changes especially the ones with myxomatous plaques, pools of mucopolysaccharide or dissection of the proximal artery.

**Table-1- Age distribution among patients with aneurysms**

| Age range (years) | No. of aneurysms | Males | Females |
|---|---|---|---|
| 10-20 | 05 | 04 | 01 |
| 21-30 | 07 | 05 | 02 |
| 31-40 | 22 | 12 | 10 |
| 41-50 | 43 | 27 | 16 |
| 51-60 | 56 | 27 | 29 |
| 61-70 | 24 | 12 | 12 |
| 71-80 | 02 | 00 | 02 |
| >80 | 01 | 00 | 01 |

**Table-2: Location of aneurysms**

| Aneurysm | A Com | ICA | MCA | P Com | PICA | Basilar | DACA |
|---|---|---|---|---|---|---|---|
| No of patients | 49 | 35 | 28 | 14 | 08 | 08 | 03 |

A Com- Anterior communicating artery
ICA- Internal cerebral artery
MCA- Middle cerebral artery
P Com- Posterior communicating artery
PICA- Posterior inferior cerebellar artery
DACA- Distal anterior cerebral artery

**Table-3: Clinical profile and risk factors of patients with multiple aneurysms**

| No. of aneurysms | Males | Females | Age41-60 years | Hypertension | Diabetes | Smoking | Alcohol |
|---|---|---|---|---|---|---|---|
| 02 | 09 | 04 | 10 | 07 | 00 | 08 | 04 |
| 03 | 00 | 02 | 01 | 00 | 00 | 00 | 00 |

**Table-4: Lipid profiles of patients (Number of samples-145)**

| | Cholesterol | Triglyceride | HDL |
|---|---|---|---|
| Normal | 44.8% | 68.3% | 64.1% |
| Abnormal | 55.2% | 31.7% | 35.9% |

**Table-5: Histopathological analysis of Biopsies**

| Age | TAM | FAM | TANM | FANM | BO |
|---|---|---|---|---|---|
| 11-20 | 01 | 01 | 00 | 00 | 01 |
| 21-30 | 01 | 02 | 00 | 01 | 01 |
| 31-40 | 02 | 00 | 01 | 01 | 02 |
| 41-50 | 07 | 03 | 00 | 03 | 02 |
| 51-60 | 10 | 07 | 00 | 03 | 01 |
| 61-70 | 00 | 02 | 00 | 00 | 01 |
| Total No. of patients (53) | 21 | 15 | 01 | 08 | 08 |

TAM- True aneurysm with mucoid change
FAM- False aneurysm with mucoid change
TANM- True aneurysm with no mucoid change
FANM- False aneurysm with no mucoid change
BO- Blood only.

**Table-6: Lipid profile of patients with biopsies (46 out of 53)**

| | TG | HDL | Total Cholesterol |
|---|---|---|---|
| Normal | 30 | 30 | 20 |
| Borderline | 08 | 13 | 18 |
| Abnormal | 07 | 03 | 08 |

TG- Triglycerides
HDL- High Density Lipoprotein

**Table-7- Risk factors in patients with/without mucoid change.**

| | Total-53 | Mucoid Changes (36) | No Mucoid Changes (17) |
|---|---|---|---|
| Females | 18 | 14 | 04 |
| Males | 35 | 22 | 13 |
| Hypertension | 17 | 14 | 03 |
| Diabetes | 03 | 01 | 02 |
| Smoking | 22 | 15 | 07 |
| Alcohol | 13 | 08 | 05 |
| Chol (=>200) | 26 | 17 | 09 |
| TG (=>150) | 15 | 10 | 05 |
| HDL (=<44) | 16 | 08 | 05 |

Chol- Total Cholesterol
TG- Triglycerides
HDL- High Density Lipoprotein

**Table-8: Clinical and biochemical parameters of patients with raised serum GAG values.**

| Total Number (73) | Age-41-60 yrs | DM | HTN | Smoking | Alcohol | Chol (>=200) | TG (>=150) | HDL (=<44) |
|---|---|---|---|---|---|---|---|---|
| Males (41) | 27 | 02 | 13 | 31 | 16 | 16 | 10 | 17 |
| Females (32) | 21 | 04 | 10 | 00 | 00 | 21 | 09 | 07 |

DM- Diabetes mellitus
HTN- Hypertension
Chol- Total cholesterol
TG- Triglycerides
HDL- High Density Lipoprotein

**Figure 1.**

**A.** Proximal artery stump shows features of marked mucoid vasculopathy and acute transmural dissection (arrows) {H & E * 125}.

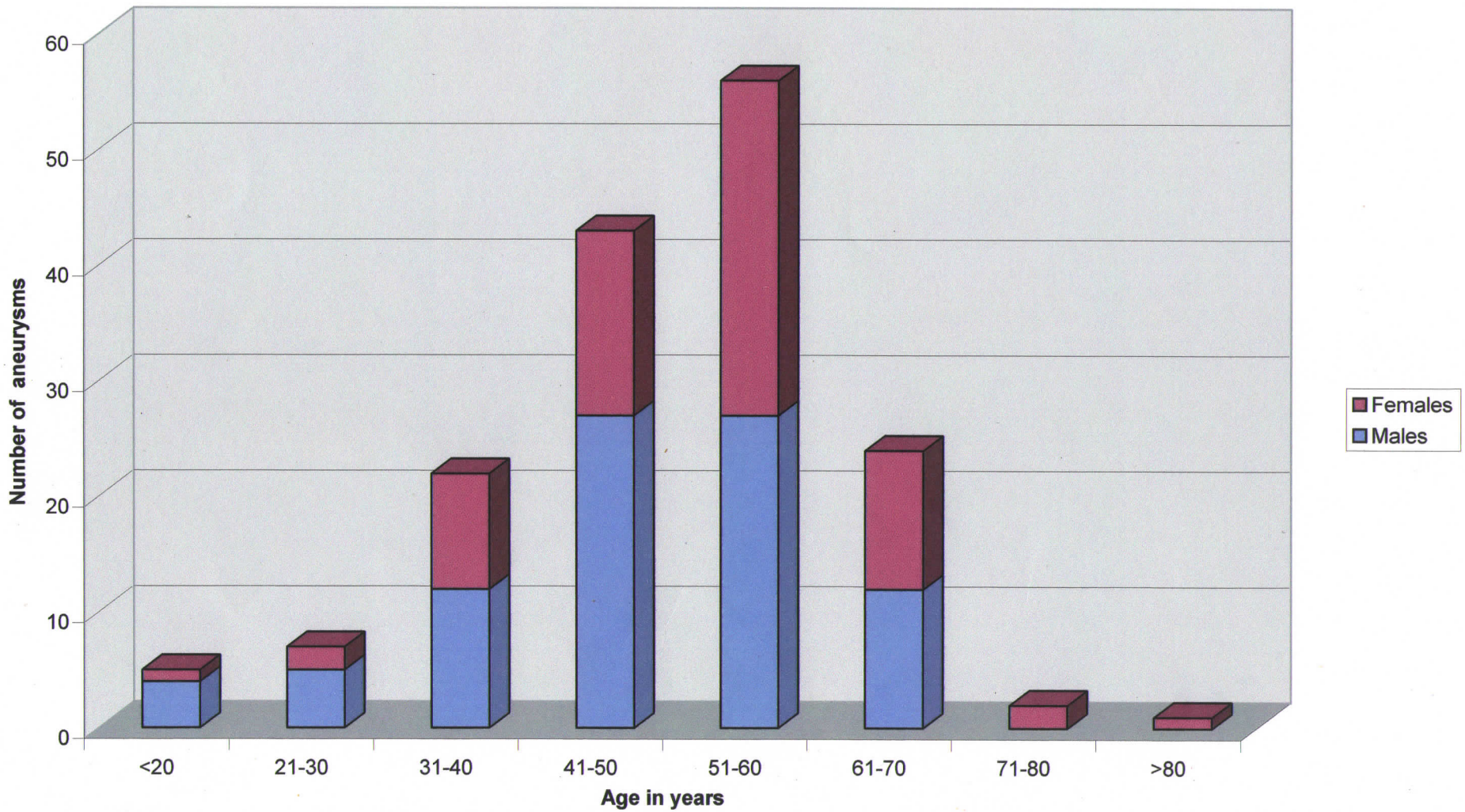
**B.** True aneurysm sac with remnant of ruptured internal elastic lamina (arrow) shows severe mucoid degenerative changes in intima and media {H & E * 125}.

**C.** Secondary false aneurysm sac at summit of true aneurysm contains organizing blood {H & E * 50}.

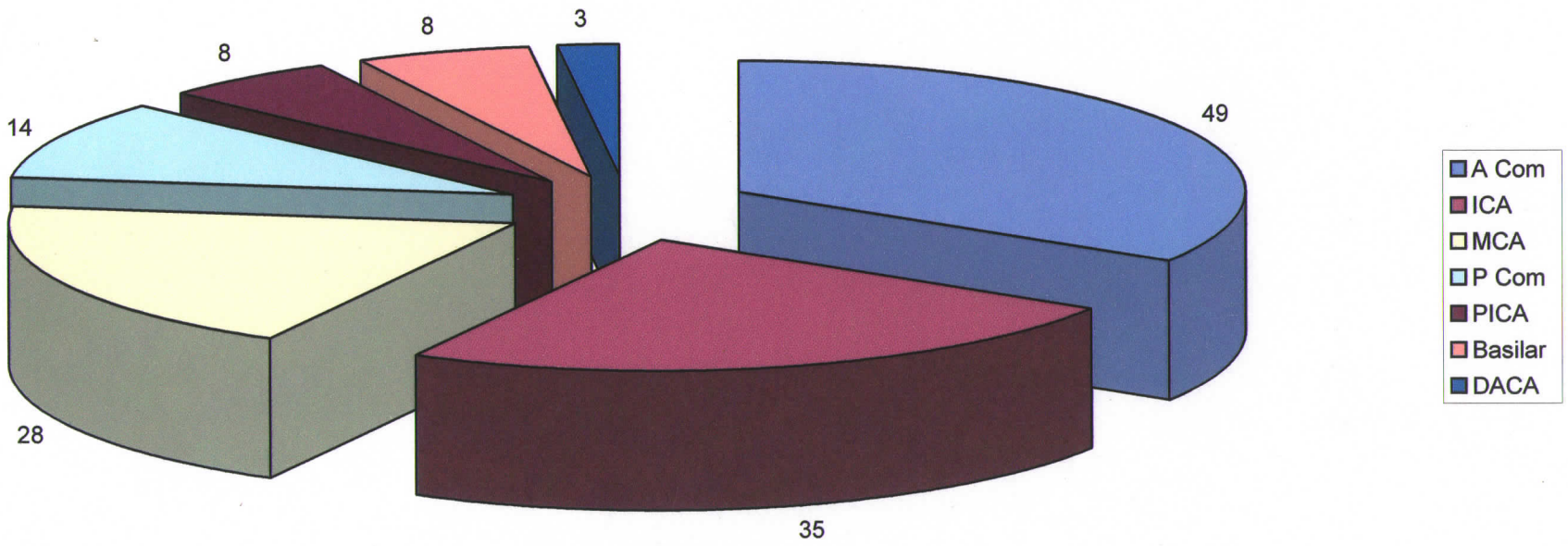
**D.** Fibromucoid plaque lining the aneurysm sac in (C), consists of numerous elongated myofibroblasts and smooth muscle cells in bundles and sheets interspersed with mucin {H & E * 510}.

**E & F.** Myxomatous plaque has hyperplastic stellate myofibroblasts within abundant pools of pale blue acid mucopolysaccharide material (E), seen as magenta colored metachromatic material in F {E: H & E * 510; F: Toluidine blue *510}.

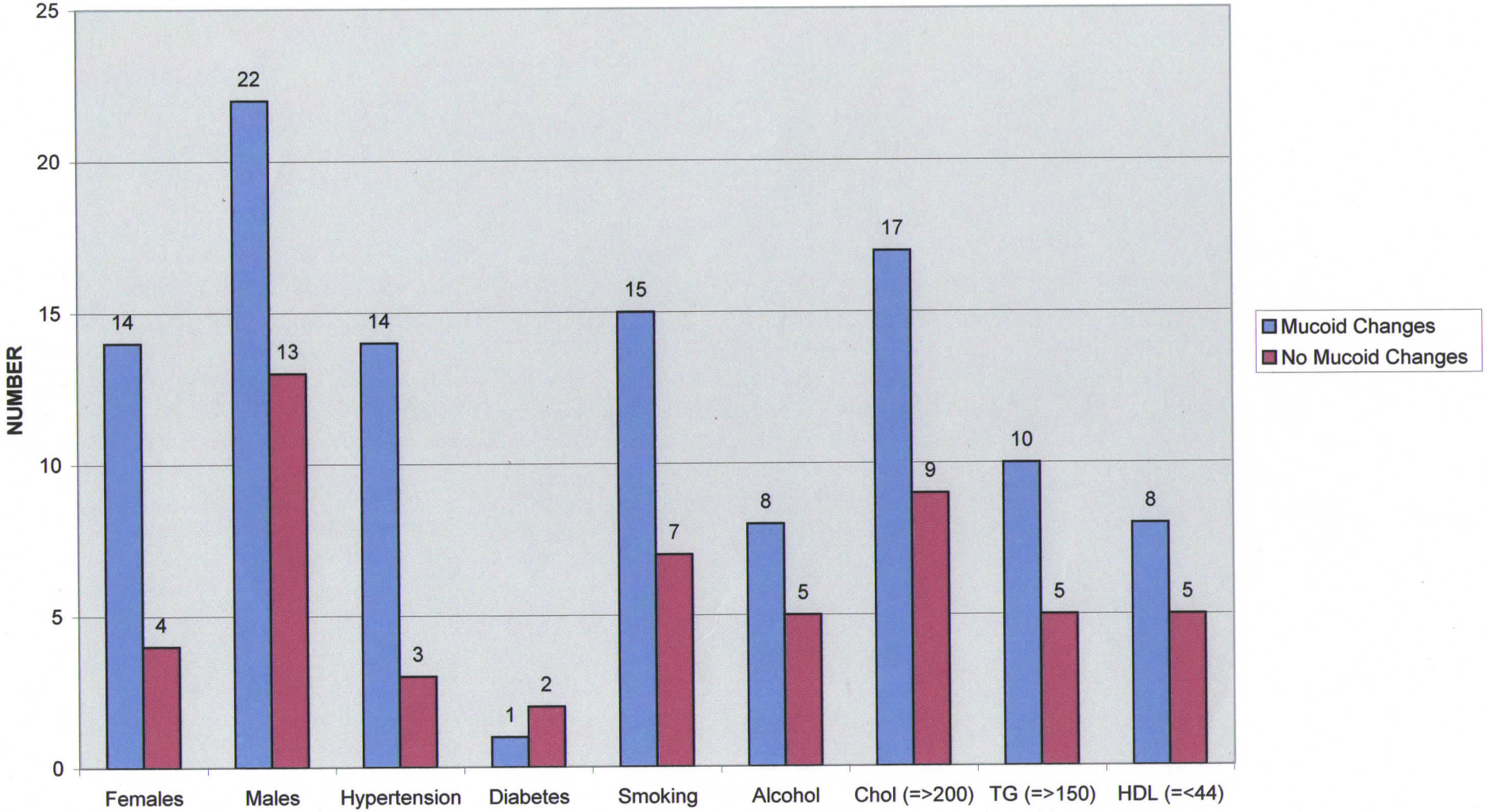
## AGE DISTRIBUTION



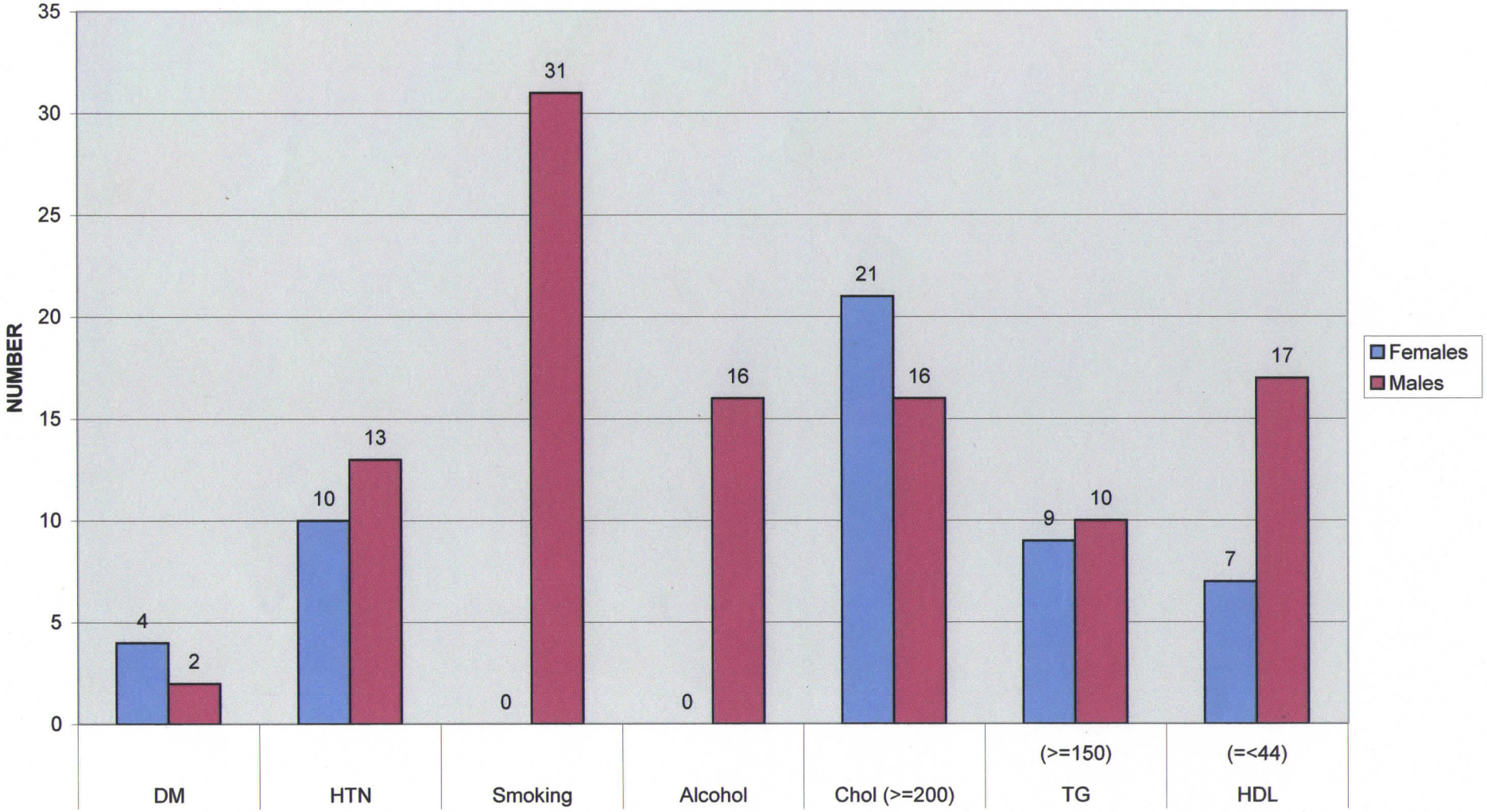
## LOCATION OF ANEURYSMS



## RISK FACTORS IN PATIENTS WITH/WITHOUT MUCOID CHANGES



## CLINICAL AND BIOCHEMICAL PARAMETERS IN PATIENTS WITH RAISED SERUM GAG VALUES



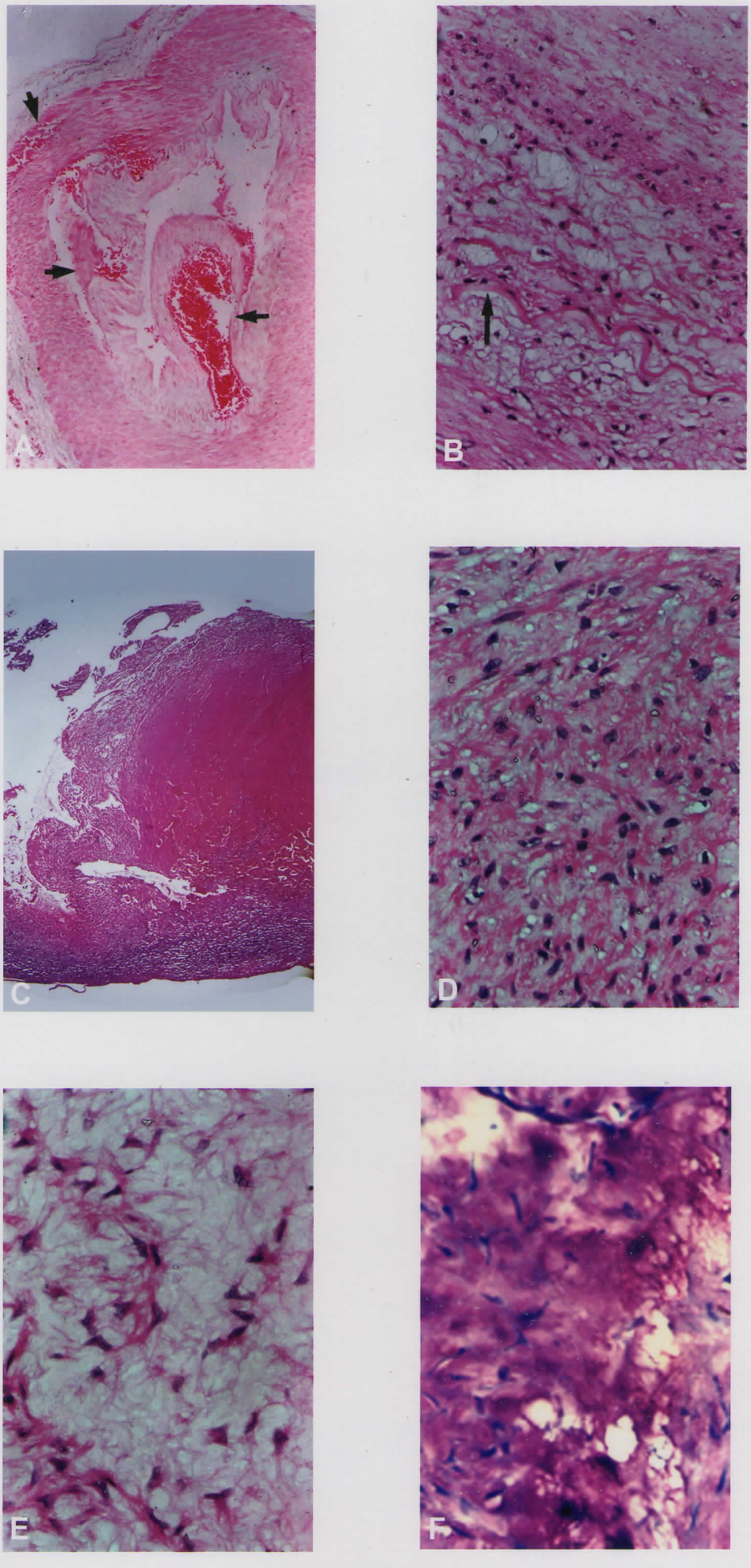



**Figure .1**

# DISCUSSION

# Discussion

Except for a few proven ones, the majority of the intracerebral aneurysms do not have a proven etiological factor. In an earlier study, mucoid degeneration was found in the aneurysm biopsies analyzed.[3] In the present study the various risk factors associated with intracerebral aneurysms and the clinicopathological correlation along with blood lipid and GAG levels has been evaluated. This study focuses on the occurrence of mucoid degeneration in the cerebral aneurysms and the various risk factors associated with it.

The commonest age group of patients with cerebral aneurysms is in the 5$^{th}$ and 6$^{th}$ decades in this study (61.87%), which is a decade earlier than that reported in the literature (6$^{th}$ and 7$^{th}$ decades).[35,10] The distribution among males and females was 54% and 46% respectively. The ratio between females and males in the cooperative study was 1.6:1 whereas in this study it is 0.8:1.[35] In this study hypertension was seen in 36.9% (59/160) and diabetes in 9.4% (15/160) and 11 patients had both preexisting hypertension and diabetes. Hypertension has been reported in 16% to 43.5% of patients with subarachnoid hemorrhage in various studies with a seven fold increased risk of causing an aneurysmal bleed.[36] Hypertension is thought to activate the initial changes in the vessel wall that lead to aneurysm formation. It may cause multiple aneurysms and may promote rupture in susceptible individuals.[10,36] Hypertension as an etiological factor for aneurysms has more positive correlation with multiple aneurysms.[21] In this study in patients with multiple aneurysms the incidence of hypertension was 46.6% (7 out of 15). In a meta-analysis it was estimated that relative risk of SAH in smokers was 2.9.[37] In various studies SAH can be attributed to smoking in 38-48% of cases.[16] In this study 57

patients (all males) were smokers out of the 160 (35%). Twenty-seven (all males) patients used to consume alcohol. Studies have shown that recent heavy alcohol consumption and long term heavy smoking are independent risk factors in a dose-response manner. Heavy alcohol use and binge drinking are associated with risk of subarachnoid hemorrhage, probably due to alcohol mediated hypertension or alterations in coagulation and cerebral blood flow.[38] The drinking habits were not analyzed further in this study. Atherosclerosis is not considered an important risk factor for cerebral aneurysms even though occasional studies mention otherwise.[39] There was no lipid deposition noted in both (earlier and current) studies from this institute

The presence of mucoid degeneration in the blood vessels and the wall of both true and false aneurysms is suggestive of an underlying metabolic disorder wherein there is deposition of excessive amounts fibromucoid and myxomatous tissue during organization of a thrombus or extravasated blood. Mucoid changes were observed in a significant number of the biopsies in this study especially myxomatous plaques. The age and gender distribution, histological features, risk factors like smoking, hypertension were similar between this study and the earlier one from this institute.[3] Mucoid degeneration has been reported from other areas also but only as sporadic cases or small number of cases. Mucoid deposition has been reported in peripheral vessels also. The histological picture in all these was deposition of mucoid material in the intima and media along with fragmentation of internal elastic lamina. The associated risk factors like smoking and hypertension might lead to further weakening and subsequently rupture of the aneurysm. Mucoid vasculopathy is a non-atherosclerotic, non-inflammatory disorder, with generalized deposition of abnormal acid mucopolysaccharides in the walls of blood vessels, associated with dystrophic changes in the elastin and collagen

in the elastin and collagen composition.[5] This disorder causes not only stenotic lesions at various sites but also causes aneurysms at sites like aorta, pulmonary artery and carotid arteries. An animal model (monkey) could establish the nutritional imbalance caused by high starch and low protein diet to be responsible for the mucoid deposition.[6] Similar conditions are described from Uganda[40] (mucoid arteriopathy and aortopathy) and South Africa[32] (intimo-medial mucoid degeneration) where the diet is similar to the one consumed by people living in this part of India.[4] A increased deposition of proteoglycans in endarterectomy coronary plaques among patients from South India has been reported by Varghese PJ, Virmani R et al[41] and has been attributed to the high carbohydrate diet intake by this population.

The deposition of mucin due an acquired disorder in protein and mucopolysaccharide metabolism, from a low protein and high starch diet might be one of the causes of weakening of the arterial wall in the patients in this study. The presence of severe forms of mucoid vasculopathy, like myxomatous plaques might represent a delayed, abnormal repair of the vessel wall and increased risk of complications like rupture, rebleed and dissection.

The serum value of GAG was elevated to a significant degree in the samples tested. In those patients whose biopsies revealed marked mucoid changes their corresponding serum GAG level was also elevated. The patients with increased serum GAG values had hypertension and smoking as significant associated risk factors. The lipid profiles in patients with raised GAG levels revealed high levels of cholesterol in 50%(37 out of 73) but there was no deposition of lipid in any of the biopsies. The HDL level was low in 24 out of 73 cases but the total

cholesterol level in 17 of them was within normal range. Turkey et al[42] have noted a similar low HDL cholesterol dyslipidemia with a diet high in starch and low in fat content.

Serum GAG values were elevated in 11 out of the 13 patients in whom biopsies showed evidence of mucoid changes. Unlike lipids, the serum GAG level changes were found to directly correlate with the deposition of mucin in the tissue samples (aneurysm biopsies).

This and the earlier study done at this institute suggest mucoid vasculopathy as an important cause of cerebral aneurysms. Serum GAG level can be used as marker to diagnose the underlying vascular lesion and metabolic disorder. These studies will help in formulating measures for the detecting the population at risk due to this metabolic disorder, and to take preventive / corrective steps for the disorder.

# CONCLUSIONS

# Conclusions

This study has shown the presence of mucoid vasculopathic changes in a significant number of aneurysms. Serum GAG levels are raised in a significant number of patients. There is a strong correlation between the serum GAG levels and mucin deposits. This being a pilot study, a larger number of GAG estimation with its subtypes (free and protein-bound) in serum and tissues (aneurysm biopsies) would help understand the disorder better. The subtypes of GAG could help in predicting the natural history of these aneurysms.

# REFERENCES

# References


1. Seppo Juvela, Kristina Poussa, Matti Porras: Factors Affecting Formation and Growth of Intracranial Aneurysms, A long term follow up study. Stroke 2001 Feb: 485-491.
2. Seppo Juvela, Matti Porras, Kristina Poussa: Natural history of unruptured intracranial aneurysms: probability of risk and risk factors for aneurysm rupture. J Neurosurgery 2000; 93:379-387.
3. Rajesh BJ, Sandhyamani S and Bhattacharya RN: Clinico-pathological study of cerebral aneurysms. Neurology India 2004; 52(1): 82-86.
4. Sandhyamani S: Mucoid vasculopathy: vascular lesions in an autopsy study. Mod Pathol 1993; 6:333-341.
5. Sandhyamani S: Mucoid Vasculopathy of unknown etiology. Angiology 1991; 42:48-51.
6. Sandhyamani S: A monkey model for mucoid vasculopathy. Int Angiol 1992; 11:256-260.
7. Sandhyamani S, Valiathan MS, Saxena HMK: Cardiovascular changes in induced malnutrition in, SERC Research highlights, Department of Science and Technology, New Delhi, Feb. 1995:29-36.
8. Niebes P, Schifflers MH. Micromethod for the determination of glycos-aminoglycans in the serum. Results from the serum of healthy and varicose subjects. Clinica Chimica Acta 1975; 62:195-202.
9. Blumenkrantz N, Asboe-Hansen G. New method for quantitative determination of uronic acids. Anal Biochem 1973; 54:484-9.

10. Bryce W, MacDonald R: Intracranial aneurysms and subarachnoid hemorrhage: An overview. Neurosurgery. Robert H Wilkins and Setti Rengachary. McGraw-Hill, New York. Second Edition, Volume II 1996,2197-2213.

11. Stehbens WE: Intracranial arterial aneurysms. In Pathology of the cerebral vessels. C. V. Mosby Company, Saint Louis 1972; 351-470.

12. Stehbens WE: Etiology of Intracranial berry aneurysms. J Neurosurgery 1989; 70:823-831.

13. Ferguson GG: Physical factors in the initiation, growth, and rupture of human intracranial aneurysms. J Neurosurgery 1972; 37:666-677.

14. E. Sander Connolly Jr, Robert A. Solomon: Management of symptomatic and asymptomatic unruptured aneurysms, In Neurosurgery Clinics of North America Vol9/Number3 July 1998:509-522.

15. Forbus WD: On the origin of miliary aneurysms of the superficial cerebral arteries. Bull Johns Hopkins Hospital 1930; 47:239-284.

16. Seppo Juvela, Matti Hillbom, Heikki Numminen and Pekka Koskinen: Cigarette Smoking and Alcohol Consumption as Risk Factors for Aneurysmal Subarachnoid Hemorrhage. Stroke 1993; 24 (5): 639-646.

17. Longstreth WT, Lorene MN, Thomas DK, and Gerald VB: Cigarette Smoking, Alcohol Use, and Subarachnoid Hemorrhage. Stroke 1992;23 (10):1242-1249.

18. Miskolczi L, Guterman LR, Flaherty JD and Hopkins LN. Saccular aneurysm induction by elastase digestion of the arterial wall: a new animal model. Neurosurgery 1998; 43:595-601.

19. Christopher L Taylor, Zhong Yuan, Warren R Selman et al: Cerebral arterial aneurysm formation and rupture in 20,767 elderly patients: hypertension and other risk factors. J Neurosurgery 1995;83:812-819.

20. Servet Inci, Spetzler RF: Intracranial aneurysms and arterial hypertension: A review and hypothesis: Surg Neurol; 53: 530-542.

21. Seppo Juvela: Risk Factors for Multiple Intracranial Aneurysms. Stroke 2000 (Feb):392-397.

22. O'Boynick P, Green D, Batintzky S, Kepes JJ, Pietak R: Aneurysm of the left middle cerebral artery caused by myxoid degeneration of the vessel wall. Stroke 1994; 25:2283-2286.

23. Renno WM, Wali MA: Ultrastructural changes in a case of mucoid degeneration of the brachial artery. Pathology 1999; 31(2): 152-157.

24. Gupta AK, Sandhyamani S, Ravimandalam K et al: Multiple pulmonary aneurysms due to mucoid vasculopathy: angiographic and histological observations. Thorac Cardiovascular Surgeon 1993;41:189-192.

25. Cooper K: Extraaortic intimo-medial mucoid degeneration: A clinicopathological study. Angiology 1993;44:477-482.

26. Abdool- Carrim AT, Robbs JV, Kadwa AM, Kenoyer G, Cooper K: Aneurysms due to intimomedial mucoid degeneration. Eur J Vasc Endovasc Surg 1996;11:324-329.

27. Tse TF, Yu DY: Unusual clinical manifestations of cystic medionecrosis: Report of a case. Am Heart J 1972;84:794-800.

28. Bahr M, Posther E, and Meyerman R: Fatal stroke in a patient with carotid and middle cerebral artery dissection associated with cystic medial necrosis. J Neurol 1996;243:722-723.

29. Mitutani T et al: Cerebral dissecting aneurysm and intimal fibroelastic thickening of cerebral arteries. Case Report. J Neurosurgery 1982;56:571-576.

30. Ide Y, Fukushima T, Yamamoto M, and Tomonaga M: Vertebral dissecting aneurysm associated with medial mucoid degeneration. Case report and review of literature. Neurol Med Chir (Tokyo) 1985;26:888-894.

31. Leu HJ: Cerebrovascular accidents resulting from segmental mediolytic arteriopathy of the cerebral arteries in young adults. Cardiovasc Surg 1994; 2:350-353.

32. Decker GAG, Samson ID, Schmaman A: Abdominal aneurysm in South African Negroes due to intimomedial mucoid degeneration. Br J Surg 1977;64:513-516.

33. Eskarasy-Lottier AC, Leu HJ, and Bassetti C et al: A case of dissection of intracranial cerebral arteries with segmental mediolytic "arteritis". Clin Neuropathol 1994;13:329-337.

34. Krex D, Schackert HK and Schackert G: genesis of Cerebral Aneurysms- An Update. Acta Neurochir (Wein) 2001 ;141:429-449.

35. Kassell NF, Torner JCX, Haley EC Jr, et al: The International Cooperative study on the timing of aneurysm surgery. Part I: Overall management results. J Neurosurgery 1990; 73:18-36.

36. Kleinpeter G, Lehr S: Is hypertension a major risk factor in aneurysmal subarachnoid hemorrhage?. Wien Klin Wochenschr. 2002 May 15;114(8-9):307-314.

37. Shinton R, Beevers G: Meta-analysis of relation between cigarette smoking and stroke. Br Med J 1989;298:789-794.

38. Stehbens WE: Histopathology of cerebral aneurysms. Arch Neurology 1963; 8: 272-285.

39. Jane Adamson, Humphries SE, Ostergaard MA et al: Are Cerebral Aneurysms Atherosclerotic? Stroke 1994;25 (5):963-966.

40. Steiner I, Thomas JD, Hutt MSR: Aortopathies in Ugandan Africans. J Pathol 1973;109:295-305.

41. Varghese PJ, Arumugham SB, Cherian KM, Walley V, Farb A and Virmani R: Atheromatous plaque reflects serum cholesterol levels: a comparative morphologic study of endarterectomy coronary atherosclerotic plaques removed from patients from the southern part of India and Caucasians from Ottawa, Canada. Clin Cardiol 1998;21(5):335-340.

42. Turkey ML, Skeaff CM, Mann JI, Cox B. The effect of low-fat, high-carbohydrate diet on serum high density lipoprotein cholesterol and triglyceride. Eur J Clin Nutr 1998; 52:728-732.