Clinico-pathological study of cerebral aneurysms

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Aims and Objectives: A clinico-pathological study of cerebral aneurysms was undertaken to understand the histopathological nature of the lesions and to ascertain possible etiological risk factors. Material and Methods: Of the 255 cases of cerebral aneurysms operated upon at our institute during the two-year period between Jan 1999 to Dec 2000, a detailed study was conducted on 57 cases where the aneurysm sac could be excised and subjected to histopathological examination. Aneurysm sacs were fixed in 10% buffered formaldehyde and processed through graded alcohol. Paraffin-embedded 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.

Results: The ages of the patients ranged from 17-65 years and there were 33 males and 24 females. Twenty-six patients were chronic smokers and 19 patients had hypertension. There were 54 saccular and 3 fusiform aneurysms, predominantly involving the anterior circulation (52 cases) than posterior circulation (5 cases). In 35 cases, histopathological studies demonstrated mucoid deposits between hyperplastic cellular elements in the true and false aneurysm wall and/or parent artery or vasavasora. The changes were associated with dystrophic changes in the internal elastic lamina.

Conclusion: Besides significant risk factors like smoking and hypertension, such mucoid vasculopathic changes may have predisposed vessels to structural weakness and aneurysm formation in our patients.

Key Words: Cerebral aneurysms, Mucoid degeneration.

Introduction

During the last 25 years, besides mycotic aneurysms,¹⁻³ a large number of cerebral aneurysms cases with no definite cause, were encountered at Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST). Although clinical aspects of cases operated upon were reported earlier,⁴ a detailed histopathological study was not carried out on them. 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.⁵⁻⁷ A clinico-pathological study was conducted to ascertain the histopathological nature and associated risk factors in cases of cerebral aneurysm admitted to SCTIMST, Trivandrum, during a 2-year period. The observations are presented in this paper.

Material and Methods

During the 2-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 mycotic aneurysm. Aneurysm sacs 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.

Results

Clinical data

There were 57 patients whose aneurysm sacs were excised during the period Jan 1999-Dec 2000 and were available for analysis. The age of the patients ranged from 17-65 years.

<table>
<thead>
<tr>
<th>Age</th>
<th>FAM</th>
<th>FANM</th>
<th>TAM</th>
<th>TANM</th>
</tr>
</thead>
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<td>0</td>
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<td>10</td>
<td>5</td>
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</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>19</td>
<td>13</td>
<td>3</td>
</tr>
</tbody>
</table>

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

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and there were 33 males and 24 females (Table 1). Twenty-six patients were chronic smokers, 19 patients had hypertension and 3 patients had diabetes mellitus. Of the 23 patients in whom lipid profiles were estimated, 5 had raised total serum cholesterol and 14 had low serum HDL-cholesterol levels. As per the gradation system used by our hospital, 19 cases belonged to the high-income category and 38 cases belonged to the lower income category. Fifty-two patients presented with subarachnoid hemorrhage and 5 patients had no demonstrated subarachnoid blood. 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. In selected cases of fusiform aneurysms, the adjoining segment of the affected vessel was also excised. Preoperative angiography had revealed vasospasm in 7 patients. Fifty-four aneurysms were saccular and 3 were fusiform (2 were vertebral artery dissecting aneurysms and 1 was M2 segment aneurysm). Thirty-nine patients were asymptomatic on follow-up, 7 patients had significant residual neurological deficits, 5 patients expired and 6 patients were lost to follow-up.

### Histopathology

Histologically, the biopsy samples were classified as: true and false aneurysms (Table 2). The histomorphological features are shown in Figure 1 and Figure 2. In 7 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 2), 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 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 vasorum in some of these cases 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 were commonly seen in patients in the 5th and 6th decades. There were 20 males and 15 females having mucoid changes. Multiple aneurysms with mucoid changes were common in females (4 cases). Middle cerebral artery aneurysms were more common in males (8 cases). Amongst the 35 cases with mucoid changes, 18 patients were chronic smokers, 15 patients were hypertensive, and 2 patients were diabetic, 2 patients had a raised serum total cholesterol level and 9 had a low serum HDL-cholesterol level (Table 2). Ten of the 19 patients in “D” group (high 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 22 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 2).

### Discussion

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 reported previously. Besides these, in a large number of cases, the exact nature and cause of 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. 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 number of cases and their association with known risk factors like hypertension and smoking. As reported in the literature aneurysmal rupture is more common in 6th and 7th decades of life however, in our study group the incidence was more in 5th and 6th decades. In our

| Table 2: 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 |
| Total Cholesterol | 5 | 2 | 1 | 1 |
| HDL-Cholesterol | 14 | 9 | 2 | 1 |

*FAM: False aneurysm with mucoid changes, †TAM: True aneurysm with mucoid changes*

Figure 2a: 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. (d: HE*24)

Figure 1a, 1b and 1c: Parent artery (a, b) and vasavasorum (c) have thick intima with vacuoles of mucoid material in intima and media between hyperplastic smooth muscles cells. The internal elastic lamina (in a, b) shows reduplication, focal thickening and fragmentation (a: HE*240, b: Verhoeff van Gieson*240, c: HE*96)

study the males were predominant, although some studies identify a clear female preponderance (1.6:1). Hypertension has been reported in about 16% to 43.5% of patients with aneurysmal subarachnoid hemorrhage. Hypertension was seen in 33.33% (19) of our cases. Smoking, another important risk factor for cerebral aneurysms was seen in 45.6% (26) of our cases. Although reported occasionally, atherosclerosis is not considered an important risk factor for cerebral aneurysms.

The etiopathogenesis of cerebral aneurysms is uncertain and the cause of subsequent rupture is not evident in all cases. The congenital or medial defect theory hypothesizes a weakness in the artery wall due to maldevelopment. 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 polyeystic kidney. Alternatively, the degenerative theory suggests an acquired defect in

Figure 2e: 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 (e: Toluidine blue*96)

Figure 2c and 2d: 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 (c). The myxomatous nodule (d) contains large pools of magenta-colored acid mucopolysaccharide material and stellate, elongated, hyperplastic myofibroblasts. The mucoid material is seen in the surface layer of endothelial cells also (c: HE*40, d: Toluidine blue*385)

the vessel wall.\textsuperscript{20-28} This theory is supported by the increased frequency of aneurysms with age, hypertension, smoking and arteriosclerosis.\textsuperscript{25} The present consensus is that atherosclerosis does not lead directly to the formation of aneurysms.\textsuperscript{25} Combinations of maldevelopment and degeneration may also exist. It is known that cerebral arteries differ from extra-craniial 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 fibrillar proteins in the matrix of the intima and media. Any alterations or damage to these vessel wall components, especially the internal elastic lamina and media, along with local hemodynamic factors can lead to the development of aneurysms.\textsuperscript{28-30} The effects of associated risk factors, particularly hypertension and smoking, may be mediated through damage to the internal elastic lamina.\textsuperscript{15,25}

A review of the 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 a small number of cases and therefore not directly comparable with our cases. Various authors used different terminologies such as cystic medial necrosis,\textsuperscript{32,33} intimal fibroelastic thickening,\textsuperscript{34} medial mucoid degeneration,\textsuperscript{35} segmental mediolytic arteriopathy,\textsuperscript{29} myxoid degeneration,\textsuperscript{27} and mediolytic arteriopathy;\textsuperscript{47} to describe the nature of the lesions in the cerebral and extracerebral cervical vasculature. In all these reports, the common finding was the deposition of mucoid material in the intima and media with fragmentation of the internal elastic lamina causing weakening of the vessel wall. Generalized involvement of the extracranial vessels in addition to cerebral vessels has been reported by some.\textsuperscript{31,37} Associated risk factors like hypertension and smoking resulted in further weakening of the wall leading to aneurysm formation, dissection and even rupture.\textsuperscript{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.\textsuperscript{2-7} Besides stenotic lesions, the condition was responsible for aneurysms at various sites, such as aorta, pulmonary artery and carotid artery.\textsuperscript{28-42} A monkey model established the role of nutritional imbalance, with low-protein high starch diets, in its etiology.\textsuperscript{43} Mucoid vasculopathy is similar to mucoid arteriopathy and aortopathy described from Uganda\textsuperscript{44,45} and to intimo-medial mucoid degeneration described from South Africa\textsuperscript{46,47} where similar diets as consumed in Kerala, may be responsible for mucoid degenerative vascular disease.\textsuperscript{49}

In this study, a significant number of patients showed dystrophic changes in the internal elastic lamina. It is well known that structural gaps in the internal elastic lamina are responsible for the development of cerebral aneurysms at bifurcation points.\textsuperscript{29} Such gaps aggravated by acquired degenerative
changes in elastic laminae may have predisposed arteries to aneurysmal dilatation at bifurcation and non-bifurcation sites in our cases. We postulate that mycotic degeneration and dystrophic changes in the internal elastic lamina in blood vessels are brought about by an acquired disorder of mucopolysaccharide and protein metabolism due to exposure to a low-protein and high-carbohydrate diet for many years. This mycotic and elastic tissue degeneration or mucoid arteriosclerotic vasculopathy, weakens the vessel wall and when combined with risk factors like hypertension and smoking, it 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 the 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.

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