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PATHOBIOLOGY OF HUMAN INTRACRANIAL SACCULAR ANEURYSMS

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Intracranial saccular aneurysms develop in the course of life in a few percent of the total population. Usually they grow slowly, remain unnoticed, but their rupture induces subarachnoid bleeding with fatal or devastating consequences. Several theories have been constructed to explain the pathomechanism of aneurysm development and rupture. Here these theories will be reviewed. The very complicated blood flow pattern in arteries at the human cerebral base, instability of collateral circulation as well as blood pressure changes can disturb normal, laminar blood flow at bifurcations. With endothelial damage, integrity of basal lamina and internal elastic lamina will also be affected. Evagination of the thin wall occurs with increasing stresses on medial elements. Any pathological factor affecting molecular structures joining connective tissue components with each other, or with the cellular structures, will promote the evagination process. With further enlargement of the sack, increasing mechanical forces make the presence of smooth muscle cells impossible in the wall. When this happens, the ability to rearrange, reorientate connective tissue fibers with the aid of active forces will be lost. Passive rearrangement of fiber structure governed by distending forces, thinning of the wall will be the result, unavoidably leading to the fatal outcome. We can conclude that current hypotheses of human intracranial saccular aneurysm development are not necessarily contradictory. Probably, they describe different factors promoting separate phases in the aneurysm development. ***Biomed Rev 2000; 11: 53-61.***

INTRODUCTION

Rupture of an intracranial aneurysm and consequent subarachnoid bleeding is a rare, but serious medical situation. It mostly affects people in the state of total well-being leaving most of its victims dead or neurologically devastated in the course of a few hours or days. The number of people affected is not too high, the incidence is a few hundred thousandths of the population a year. That means a few hundred cases in a country of the size of Hungary with about of 10 million population. The economic and human consequences, however, are very serious. Repeated neurosurgical treatment, prolonged intensive care, long lasting rehabilitation and large losses in deaths and working capacity make this disease an important entry in all health statistics. Limits of therapy stress the significance of preventive measures. Slow, unnoticed development of the intracranial aneurysm sack, however, with no or with uncharacteristic symptoms make its recognition before rupture a rare but fortunate occasion (1-3).

Careful pathologic studies on large population are alarming.

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Up to 8 % of the whole human population may harbor an aneurysm sack of the arteries of the cerebral base in some form in the course of his/her life (3-9). The arteries of the human cerebral base, to some degree, seem to be biologically prone for saccular aneurysm development. Recent studies revealed important pathobiological mechanisms leading to intracranial aneurysm development and rupture. They will be discussed in this article.

MACROSCOPIC ANATOMY OF INTRACRANIAL SACCULAR ANEURYSMS

Typically, intracranial aneurysms are sitting in the bifurcations of the arteries of the cerebral base. Their entrance is in the fork of the two daughter vessels. The most frequent locations are the bifurcations of the anterior communicating artery and the medial and the anterior cerebral arteries. Morphologically, most intracranial aneurysms are of the saccular type, that is, they form a sharply delineated evagination of the vessel wall with a narrow neck and a wide blind sack. Fusiform aneurysms, when the arterial wall forms a morphological dilation with some circular symmetry is less frequent at the base of the brain and mostly affects the basilar artery. This latter form seems to be a different pathological entity and will not be dealt with in this article. The size of saccular aneurysms is very variable, spanning from 1- 2 mm to giant aneurysms with diameters of 15-20 mm (4,6,7,10). Their diameter is increasing in time, and larger aneurysms will rupture with higher probability (11-13). With increasing size they can compress meningeal and neural structures causing headache and focal neurological symptoms, which can lead to their timely recognition. As they increase in size, the apical part of the sack is getting thinner. Rupture usually occurs at the apex of the sack. Development of multiple aneurysms is not the rule, but is not unfrequent. In the lumen of the sack, in most cases, fluid blood can be found, which is continuous with blood in the parent vessel through the neck portion. In some cases the sack can be filled with coagulated blood which is loosely or tightly attached to the wall (4,6,7,10).

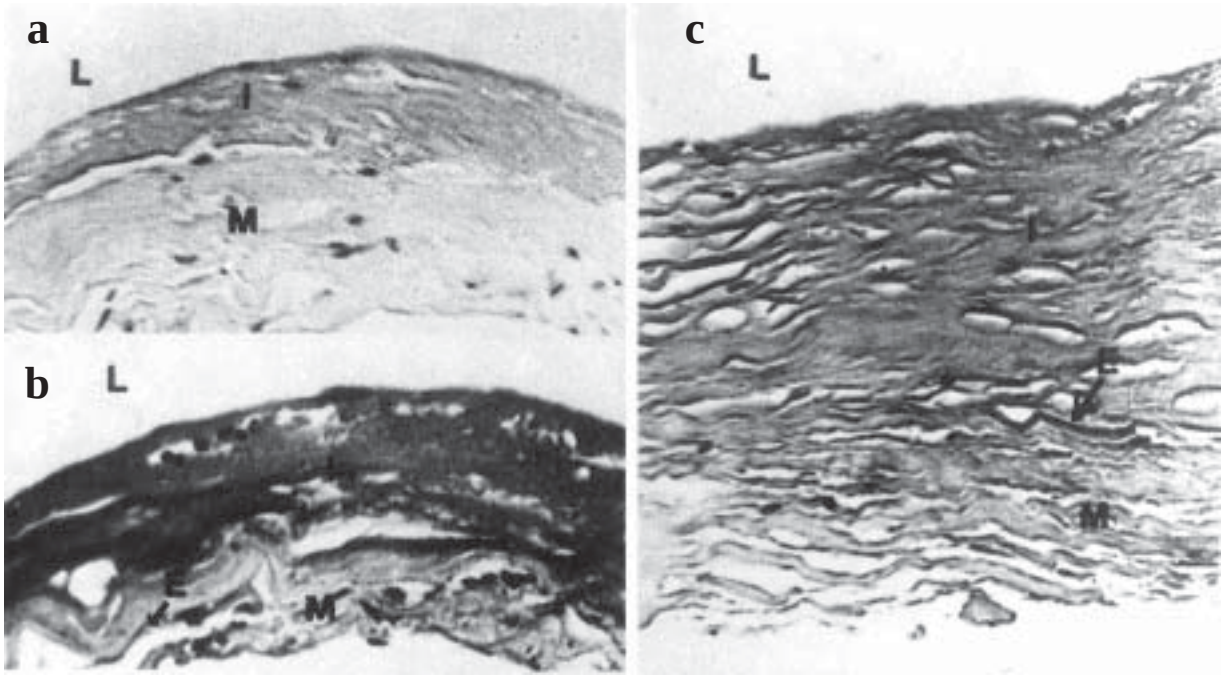

Figure 1. *Light micrographs of aneurysm tissue. A characteristic difference between saccular aneurysm tissue and normal cerebral arterial wall is a total absence of smooth muscle cells.* ***(a)*** *The vessel wall is homogenous, almost acellular. Hyaline degeneration in the intima (I) and fibrosis in the media (M) (hematoxylin-eosin staining).* ***(b)*** *Dark stained hyaline substance in the intima (I) and elastic fragments (E) in the media (M) (alcian blue staining for glycosaminoglycans).* ***(c)*** *Few fragments of elastic fibers (E) at the border of intima (I) and media (M). The wall consists mostly of hyaline substance and collagen fibres (resorcin-fuschin-van Gieson staining).*

HISTOLOGY OF INTRACRANIAL SACCULAR ANEURYSMS

The forks of arterial bifurcations, where the saccular aneurysms develop, are histologically very characteristic sites. The layers normally forming the arterial wall are inherently disturbed (14-17). At the carina subintimal cushions appear in early life. The texture of the internal elastic lamina and of the smooth muscle layers of the media forms much more complicated patterns than in unbranching artery. The histological structure of the aneurysm wall is totally different from that of the normal arterial wall. Usually there is a well developed subintimal hyperplasia. The internal elastic lamina is entirely missing or disrupted. Very characteristic is the disappearance of smooth muscle cells and a general scarcity of cellular elements. Disorientation of reticular and collagen fibers seems to be connected with the aneurysm pathomechanism (14,16-22) (Fig. 1).

MORPHOLOGICAL COMPLEXITY OF THE ARTERIES OF THE HUMAN CEREBRAL BASE

Aneurysms of the saccular type while frequently occur in arteries of the cerebral base are uncommon in other arteries. Some hypotheses connect saccular aneurysm development to the morphological characteristics of these arteries. Biological development of the base of the human skull made the carotid siphon a hemodynamically unique place. Most blood entering the skull must pass through a curved bony channel, where pulsations can not be cushioned with surrounding soft tissue. The four large arteries entering the skull form the collateral system of the circle of Willis. There are large individual variations in the development of the collateral branches of this system, high degree of asymmetry is very frequent. Histologically, intracranial arteries are thin walled muscular arteries. Such histological characteristics as thinness of the wall, scarcity of elastic elements, and as it is in the case of the basal arteries, lack of mechanical support from the surrounding structures are thought to be connected with their proneness to develop saccular aneurysms (17,23-25).

HEMODYNAMIC CHARACTERISTICS OF THE ARTERIES OF THE HUMAN CEREBRAL BASE

Complicated shape of the lumen determines complicated pattern of blood flow. Frequent changes of angle of flow, frequent bifurcations at unusual angles, blood flow instabilities at collaterals, and turbulences, all these factors can induce disturbance in shear rate at the endothelial surface. Arterial hypertension, especially its unstable form will elevate circumferential wall stress in these thin walled arteries. One theory of intracranial saccular aneurysm development emphasizes the significance of altered shear rate at the endothelial surface (16-18,20,24,26-30). Morphological malformations of the circle of Willis are frequently accompanied with the development of aneurysms. Arterial hypertension increases the incidence of cerebral aneurysms according to large statistical materials (3,31,31a). Intracranial aneurysms could be successfully induced in rat experiments by increasing the arterial pressure and by increasing collateral flow in the branches of the circle of Willis by ligating one of the carotid arteries. The fact that the lathyrogenic factor beta aminopropionate could be left out from the regimen, gives a direct proof, that hemodynamic factors alone, without any contribution of connective tissue molecular damage can induce cerebral aneurysms (29,32-38). Based on these animal experiments, a partial validity of the classic hemodynamic theory (17,26) can not be questioned. Endothelial damage is among the first steps of aneurysm development in these animal experiments (29,37). Despite some views that aneurysm development in general should be associated with local atherosclerotic changes, most authors seem to agree that intracranial saccular aneurysms are a different entity. However, such views have been reinforced by some new clinical chemistry data showing a correlation between plasma lipoprotein(a) and the incidence of intracranial saccular aneurysms; this may implicate some common pathomechanisms (39; 39a,b for aortic aneurysms). Filtrated through the damaged endothelium, growth factors can also enter the wall. The presence of vascular endothelial growth factor and basic fibroblast growth factor in aneurysm tissue has been shown in a recent work (40).

HEMODYNAMIC PATTERNS IN THE ANEURYSM SACK

The cavity of the aneurysm sack is in connection with the lumen of the parent vessel through the neck portion. Arterial blood pressure and its changes are freely transmitted to the wall of the sack, causing a mechanical overburden on the wall tissue, which increases with of the distending radius of the sack (41). The few available data on blood flow pattern in the sack demonstrate circular flow with turbulence. Disturbance of endothelial shear rate in the sack itself seems to be evident. Subintimal hyperplasia found in the sack may be the consequence of this disturbed blood flow pattern (28,30,42).

GENETICS OF INTRACRANIAL SACCULAR ANEURYSMS

Several studies show that other cerebral vessels and even extracranial vessels are also affected in patients with cerebral aneurysm. Thus, this disease can be considered more as a general pathological alteration of the whole arterial system than a simple local failure of the wall. In a study from our and other laboratories, thickening of the wall of the anterior cerebral artery directly not affected by the trait was found (43-46). The thickening of the wall of other cerebral vessels may be induced by some compensatory mechanisms triggered

by the inferior mechanical quality of the wall also found in some studies. The decreased lumen of upper member artery may reflect some inherited morphological alteration in vascular development (46). Connective tissue disorders could also be identified in intracranial or extracranial vessels directly not affected by the aneurysm formation (19,44,47-49).

Familial occurence can be verified in up to 20 % of all cases, but has been searched without success in the remaining ones (2,50-53). According to some authors, the familial form can be defined as a different entity. Females are more affected in this type, the location of the sack is also different: branches of the medial cerebral artery are more frequently involved and the development of multiple aneurysms is more probable (50,51,53).

An interesting topic directly proving the connection of the disease with genetic factors is the high probability of intracranial aneurysm development in known inherited connective tissue disorders (53,54). In autosomal dominant polycystic kidney disease the occurrence of intracranial aneurysm can be shown in about one quater of the cases (2). The molecular damage involves the protein polycystin, which is a membrane protein thought to play an important role in joining cellular elements with surrounding connective tissue (53-55). In Ehlers-Danlos syndrome, the gene of collagen type III is damaged. This molecular trait has also been related to aneurysm development (53,54). Collagen type III is a main component of extracellular matrix of distensible tissues (54). Further, an increased incidence of intracranial aneurysms in Marfan syndrome is stressed by some authors (53,54), but one large statistical study did not show such correspondence (56). Mutations of the gene encoding the protein fibrillin-1 are in the background. Fibrillin-1 is an important glycoprotein of the extracellular matrix. Being a basic constituent of microfibrils, it provides a scaffolding for the elastic fibers (53,54,57). In neurofibromatosis, which is also connected to intracranial aneurysm development, the molecular damage affects the gene of the protein neurofibromin. This protein is supposed to take part in the regulation of growth of connective tissue by affecting microtubular arrangement inside the cells (53,54,58). There are also some other scattered records on the connection of other inherited connective tissue molecular diseases with intracranial aneurysms (53,54). A molecular deficiency of collagen type III should be in the background of most intracranial aneurysm cases (45,59,60,61). An increased elasticity and reduced collagen type III content was found in a part of unaffected cerebral arteries by Ostergard *et al* (43). Controlled molecular biological studies, however, excluded the possibility that a molecular damage to the collagen type III gene would be in the background in most of cerebral aneurysm disease cases (62,63). Reduced expression of the gene, however, can not be entirely excluded based on these studies.

According to a recent report, frequent coincidence of intracranial saccular aneurysms with malformations of the large vessels may be connected with disturbance of the development of the embryonic neural crest (64). In addition, the development of saccular aneurysm has been connected to medial defects in cerebral base arteries of embryologic origin (14,24,65). However, recent work by Tsuruda *et al* (66) has shown that such defects can be observed at the lateral sides of the bifurcations only, while saccular aneurysms consequently develop at the carina. The possible involvement of genetic factors in aneurysm development is further supported by findings that different rat strains are differently sensitive to aneurysm development induced by hemodynamic factors (67).

The search for the supposed intracranial aneurysm gene is underway. Family studies did not give a resolute answer concerning a potential inheritance pattern, even when sufficient pedigrees could be obtained. Perhaps, a low expression of the “intracranial aneurysm gene” is responsible for the failure to establish the genetic pattern (50,51,53,54).

ALTERATIONS IN CONNECTIVE TISSUE AND IN VASCULAR MECHANICS

Several authors have described different types of connective tissue derangement in the aneurysm both in intracranial and extracranial arteries. Decreased amount of collagen in intracranial arteries, and a disoriented pattern of its distribution are described by some authors, while denied by others (43,49,68,69). Biochemically, one type of covalent crosslinks, which binds collagen molecules together, is reduced (69). Supposed alterations in collagen type III structure and amount were discussed above. Recently, Chyatte and Lewis (70) suggested that an increased serum gelatinase activity is connected with occurence of intracranial aneurysms.

Arteries of the cerebral base are characteristically scant of elastic elements. These latter are usually restricted to the internal elastic lamina. Pathological alterations of elastic tissue seem to be a consequent feature in cerebral aneurysm disease. Unusual fenestrations of the internal elastic lamina in intracranial arteries, large fenestrae at the site of aneurysm development, derangement and fragmentation of elastic fibers are described (16,18,20,29,37,71). Increased level of plasma elastase of leukocyte origin was found in aneurysm patients (48,72). In aneurysm patients, the amount of reticular fibers is decreased in intracranial vessels. Their orientation pattern is disturbed (19,44,47). The distribution of collagen type IV also shows a dispersed, scattered and disorientated pattern in aneurysm tissue (40).

According to immunohistochemical studies, the pattern of distribution of the extracellular protein fibronectin during intracranial aneurysm development is also disturbed. Fibronectin is a main component of anchoring structures, which bind connective tissue components to the cell membrane

and cytoskeletal structures (27,40).

Taking into consideration the wide range of supposed connective tissue disorders observed by a series of authors, changes in arterial wall elasticity in aneurysm patients, in unaffected intracranial and extracranial arteries are surprisingly limited (45,46,73). Thus, the molecular damage, which can be suspected based on the above described observations, will spare molecular stretches of the connective tissue elements, whose steric conformation changes determine passive elasticity of the wall (74). At the same time the aneurysm sack itself is formed from tissue elements with inferior mechanical quality. Tensile strength, elastic moduli and viscosity are decreased in comparison with unaffected intracranial arterial wall. With enlargement of the sack, thinning of the wall at the tip of the sack with reorientation of the fiber structure may occur. In this process mechanical parameters are improving in the meridional direction, but at the expense, that the tissue ruptures at lower strains in the circumferential direction (74).

PROPOSED NATURAL HISTORY OF ANEURYSM SACK DEVELOPMENT

Based on direct observations, it is very difficult to give a coherent picture about the chain of events leading to intracranial saccular aneurysm development and rupture. Pathological studies are mostly done on the ruptured aneurysm sack. Early phases of aneurysm development can be studied in the case of multiple aneurysms as well as on aneurysmatic evaginations of intracranial arteries found accidentally at autopsy. These latter are thought to be early forms of aneurysm sack development (3,75). Aneurysm development as a function of time can be studied in experimental animal studies (32-38).

Current views on aneurysm formation (discussed above) are not contradictory. They can be unified into a coherent picture as follows: animal experiments clearly show that hemodynamic factors alone (hypertension, increased shear stress) are sufficient to initiate the intracranial aneurysm development (32-38). Intimal damage at bifurcations will affect basal lamina and internal elastic lamina, some components of which are synthesized by the endothelial cells themselves (17,18,20,24,26-30,37). Extravasation of proteolytic enzymes, lipids and growth factors into the vascular wall may further aggravate the situation (39,40,48,70,72). With the disintegration of the internal elastic lamina, pulsative mechanical forces will be transmitted to the outer layers of the vessel wall causing their localized evagination. Any disadvantageous alteration in connective tissue molecular buildup can be expected to speed up the local evagination process. The different genetic diseases involving molecules, which bind the connective tissue components with each other or with the cellular elements may exert their effect at this step (2,53-58). With increasing inner radius circumferential wall stress also increases. This forms a classical positive feedback mechanism in aneurysm formation (11,12). As stresses and pressures increase in the wall of the developing aneurysm sack, the smooth muscle cells may loose their habitat they can live in. With the loss of these cells the possibility for active reorientation of connective tissue fibers will be lost. Disorganization of fibronectin and reticular, elastic and collagen fibers will be the result (16,18-20,22,27,37, 40,43,44,47,49,68,71,76). After smooth muscle cell disappearance, slow viscotic dilatation of the wall can go on unopposed (41). At the apex, thinning of the wall will occur. At the same time passive forces reorientate the fiber structure in a sterically inhomogenous manner (74). As a result of this fiber reorientation, the tissue close to the apex ruptures at low distending strains in the circumferential direction. Ultimately, that will induce the rupture of the sack. The pathomechanism, as suggested above, incorporates all known main factors of our present knowledge on intracranial aneurysm development.

PATHOPHYSIOLOGICAL CONSEQUENCES OF INTRACRANIAL SACCULAR ANEURYSM DEVELOPMENT AND RUPTURE

The unruptured aneurysm sack in most cases is asymptomatic, and preventive surgical procedures can not be done in time. In some cases headache and focal symptoms affecting the cranial nerves and basal cerebral structures are in the anamnesis. At rupture, spilled blood enters the subarachnoidal space causing very serious sudden headache, meningeal symptoms, brain stem cranial nerve paralysis, and, in most cases, loss of consciousness and coma. Death occurs before the patient reaches the neurosurgical facility in half of the cases (3).

In more than half of the survivors of the first days one interesting sequale is the development of the cerebral vasospasm. This dreadful condition develops on days 4-10 after subarachnoidal bleeding. For some reason the cerebral arterial trunk, the adventitia of which is embedded in the hemorrhage, will spastically constrict substantially reducing blood flow to large parts of the brain. The pathomechanism of the development of vasospasm is still not known. Different hypotheses raised the possibility that oxygenated hemoglobin, serotonin, thromboxane from thrombocytes, blood borne growth factors or immunological factors should be responsible for its development. Vasodilators can be used for treatment with some success (23,77-86).

Despite all expensive efforts, about third of the patients reaching the hospital alive will die after subarachnoidal bleeding. A further third of the survivors will have serious neurological consequences (2). Surgical clamping of the unruptured aneurysm sack can prevent aneurysm rupture and

subarachnoidal bleeding, but is rarely done, because of the lack early symptoms. This outlines the significance to identify the part of the human population, which is most endangered by this trait. Better knowledge of the pathobiology of intracranial aneurysms will probably derived from further genetic, clinical chemistry and other laboratory studies. These may also provide some insights into the possible involvement of fibrinolytic gene expression (39a), inflammatory and immune cells (39b), and matrix metalloproteinases (87) in the development and complication of intracranial saccular aneurysms.

CONCLUSION

We think that current hypotheses of human intracranial saccular aneurysm development are not contradictory. Probably, they describe different factors promoting separate phases in aneurysm development. The very complicated blood flow pattern in arteries at the human cerebral base, instability of collateral circulation as well as blood pressure changes can disturb normal, laminar blood flow at bifurcations. With endothelial damage, integrity of basal lamina and internal elastic lamina will also be affected. Evagination of the thin cerebral artery wall occurs with increasing stresses on medial elements. Any pathological factor affecting molecular structures joining connective tissue elements with each other or with the cellular components will promote the evagination process. With further enlargement of the sack, increasing mechanical forces will make the presence of smooth muscle cells impossible in the wall. The ability to rearrange, reorientate connective tissue fibers with the aid of active forces will be lost. Under the effect of large, unopposed distending forces, passive rearrangement of fiber structure, thinning of the wall will be the result unavoidably leading to the fatal outcome.

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