Intracranial aneurysms and connective tissue disorders
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The pathogenesis of intracranial aneurysms

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Introduction

Every year in the Netherlands approximately 900 people have a subarachnoid haemorrhage; the majority is caused by rupture of an intracranial aneurysm. Mortality of the subarachnoid haemorrhages is high (± 50%) during the first month, and approximately 10% die before hospital admission. A large proportion of survivors remains disabled. Despite developments in the areas of diagnostics, neurosurgery, and neuroanesthesitics the mortality of aneurysmal subarachnoid haemorrhages has hardly decreased. Health benefit can be achieved by detection and treatment of intracranial aneurysms before rupture, but only if mortality and morbidity after treatment for unruptured intracranial aneurysms is low. Knowledge of the pathogenesis of intracranial aneurysms and risk factors for development of intracranial aneurysms may improve the detection of people who are at high risk of harboring an intracranial aneurysm.

The structure of an intracranial aneurysm

The wall of an intracranial artery consists of an inner (intima), middle (media) and an outer (adventitia) layer. The internal elastic membrane lies between the intima and media. This layer is important when the strain on the arterial wall becomes high. The media consists of smooth muscle cells and connective tissue. The adventitia is composed of loose connective tissue containing small vessels. In contrast to extracranial arteries, intracranial arteries have no external elastic membrane, a thinner media, and a thinner and looser adventitia.

The wall of an intracranial aneurysm has hardly any structure, consists mainly of connective tissue with an absent or fragmented internal elastic membrane.

Risk factors

Epidemiological studies have identified several risk factors for the development of intracranial aneurysms such as cigarette smoking, a positive family history, hypertension, postmenopause and heavy drinking.

Several retrospective patient based, and prospective population based studies emphasize the importance of hypertension as a risk factor for development of intracranial aneurysms. However, during the last decades,
when there was a substantial reduction in the incidence of strokes in general, perhaps due to improved treatment of hypertension, no reduction in the occurrence of subarachnoid haemorrhages was observed.\textsuperscript{16,17} Furthermore, aneurysmal subarachnoid haemorrhages is often observed in the absence of hypertension.

Cigarette smoking reduces the effectiveness of $\alpha_1$-antitrypsin, an important inhibitor of proteolytic enzymes (e.g. elastase), which degrades amongst others the connective tissue of the arterial vessel wall.\textsuperscript{18} Heavy drinking is associated with subarachnoid haemorrhages; one hypothesis suggests a causal relation through hypertension.\textsuperscript{19}

A positive family history for subarachnoid haemorrhages is associated with a four times increased risk for having a subarachnoid haemorrhage.\textsuperscript{20} It is uncertain if this increased risk is caused by hereditary (e.g. arterial wall defect) or environmental (e.g. toxic influence) factors.

**Diseases associated with intracranial aneurysm**

In some patients with arteriovenous malformations angiography may also reveal an intracranial aneurysm. The majority of these intracranial aneurysms is located on the arterial route supplying the arteriovenous malformation, suggesting that increased blood flow is relevant in the development of intracranial aneurysms.\textsuperscript{21-24}

Intracranial aneurysms have been observed in patients with connective tissue disorders such as Marfan syndrome,\textsuperscript{25,26} Ehlers Danlos Syndrome (EDS) type IV,\textsuperscript{27,28} and Pseudoxanthoma Elasticum.\textsuperscript{29} In EDS type IV and Marfan syndrome the defective protein has been identified as respectively type III collagen and fibrillin\textsuperscript{30,31}, which are constituents of the arterial vessel wall.\textsuperscript{32-33} Therefore connective tissue disorders may cause structural (intrinsic) defects in the vessel wall leading to the formation of intracranial aneurysms.

Asymptomatic intracranial aneurysms are found in 5 to 10% of patients with autosomal dominant polycystic kidney disease (ADKP).\textsuperscript{34-36} In ADKP, hypertension is not the only factor in the formation of intracranial aneurysms. Some patients with ADKP have an aneurysmal SAH before hypertension develops.\textsuperscript{37} An intrinsic factor or a vessel wall defect may therefor also be associated with the formation of intracranial aneurysm in these patients. Polycystin-1 (the product of the PKD1 gene; the gene most frequently involved
in ADKP) has been demonstrated, using antibodies, in the vessel wall of intracranial arteries.\textsuperscript{38}

**Experimental approach for the induction of intracranial aneurysms**

Ferguson investigated the role of turbulence in aneurysm formation using a model with glass "cerebral" vessels.\textsuperscript{39} In normal bifurcations turbulence was not a factor leading to hemodynamic stress at the apex, where most aneurysms arise, but impingement of the central fluid streams may cause local vessel weakness.\textsuperscript{39}

Hassler was the first to induce cerebral aneurysms by increasing hemodynamic stress in animals through carotid ligation.\textsuperscript{40} Subsequently, in addition to carotid ligation, arterial hypertension was induced by ligating the branches of the renal arteries, and by feeding the animals with β-aminopropionitrile (BAPN) which inhibits cross-link formation of elastin and collagen in tissue.\textsuperscript{41,42} With this method, formation of intracranial aneurysms was induced in 6 of 7 monkeys (5 saccular, 5 fusiform, and 3 aneurysmal dilatations). Vessel wall changes were classified based on light microscopic findings into three stages: sequential disappearance of the internal elastic lamina, followed by thinning and dilatation of the wall and finally formation of an aneurysm.\textsuperscript{41,42}

Aneurysms can also be induced, without hemodynamic stress, using local application of elastase. Histologically these aneurysms resemble intracranial aneurysms in man.\textsuperscript{43}

**Hypotheses on the pathogenesis of intracranial aneurysms**

Several hypotheses on the development of intracranial aneurysms have been formulated. The formation of an intracranial aneurysm has been related to "medial defects", hemodynamic stress, but is nowadays regarded as a multifactorial process.

Intracranial aneurysms have been thought to be formed in the region of the "medial gaps" and were therefore considered to be "congenital". These medial defects are gaps in the media at bifurcations of normal arteries of the
circle of Willis. However, these "media defects" were also encountered in other extracranial arteries, and the distribution of these defects is different from that of intracranial aneurysms, since the defects are usually located at the lateral angles whereas intracranial aneurysms predominantly arise from the apices of the bifurcation. Nowadays, these medial defects are regarded as part of the normal ontogenesis of vessel walls.

Another hypothesis is that the development of intracranial aneurysms is dependent on a degenerative ("acquired") process, probably hemodynamic stress, possibly arterial hypertension. The experiments of Hassler, the relationship between arteriovenous malformations and intracranial aneurysms, the frequency of intracranial aneurysms increasing with age, and the association with hypertension are compatible with this concept. However, the importance of arterial hypertension as a risk factor for the development of intracranial aneurysms appears to be modest since not all patients with subarachnoid hemorrhages have arterial hypertension, with frequencies of hypertension ranging between 39 and 92%.

Nowadays the development of an intracranial aneurysm is regarded as a multifactorial process in which both intrinsic (vessel wall abnormalities) and extrinsic (hemodynamic) factors play a role. The following sequence of events is the most likely; hemodynamic stress causes degenerative changes in the endothelial layer (hypertension may increase the damage). Subsequently, the internal lamina elastica degenerates which results in pressure on the arterial wall and a reduced strength of the arterial wall increases the propensity for aneurysm formation which finally occurs.

In some patients the reduced strength of the arterial vessel wall is possibly caused by a reduced type III collagen production. However, in the majority of patients with an intracranial aneurysm this "intrinsic factor" is unknown. Increased activity of proteolytic enzymes e.g. elastase is another candidate for the role of intrinsic factor.

References


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