Intracranial aneurysms and connective tissue disorders

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General introduction
Introduction

Rupture of an intracranial aneurysm results in a haemorrhage with often devastating effects. The haemorrhage is usually located in the subarachnoidal space but it may also be present in the ventricles, intracerebrally or in the subdural space. A ruptured intracranial aneurysm frequently leads to death (in approximately 50% of cases), and a large proportion of the survivors (10-20%) remains disabled. In the last decades these figures did hardly change despite developments in neuro-anaesthesia and neurosurgery. The high mortality is for a large proportion attributable to severe brain damage caused by the initial haemorrhage. Improvement in outcome may therefore be achieved by early detection and obliteration of the aneurysm before rupture. Figures of complications (death or neurological deficits) after surgery for unruptured intracranial aneurysms are considerably higher than previously thought. A meta-analysis showed figures for mortality of 2.6% and for morbidity of 10.9%. Similar figures were reported recently by an international study group. Therefore it is important to investigate if better results can be achieved by using other techniques such as endovascular occlusion of the aneurysm with coils.

The formation of intracranial aneurysms has been related to "medial defects", and hemodynamic stress. At present the development of intracranial aneurysms is regarded as a multifactorial process in which both intrinsic (vessel wall weakness) and extrinsic (hemodynamic) factors play a role. Intrinsic factors may be related to connective tissue disorders since associations have been reported between intracranial aneurysms and Marfan syndrome, pseudoxanthoma elasticum, and Ehlers Danlos syndrome type IV. The latter is a connective tissue disease which is characterized by genetically determined defects of type III collagen due to a decreased type III procollagen production or a production of structurally altered type III procollagen. Ehlers Danlos syndrome type IV has been reported to be associated with carotid-cavernous fistulas, arterial dissections, and intracranial aneurysms. Type III collagen is very firm and responsible for the tensile strength of the arteries, especially when the strain on the vessel wall becomes high. Several small studies have demonstrated a possible relationship between type III collagen deficiency or unstable type III collagen and intracranial aneurysms.

About 5-10% of patients have a positive family history for intracranial aneurysms. The intrinsic factor in the pathogenesis of intracranial aneurysms may be a type III collagen deficiency, and this may also be the familial factor.
Aims and outlines of this thesis

The subject of this thesis was to investigate the intrinsic factors in the pathogenesis of intracranial aneurysms. Therefore the relationship between intracranial aneurysms and the connective tissue disorders pseudoxanthoma elasticum, and Marfan syndrome was studied. Furthermore studies were performed to determine if a type III collagen deficiency is related to the formation of intracranial aneurysms.

**Chapter 1** is a review of the pathogenesis of intracranial aneurysms. In 135 patients with Marfan syndrome (*chapter 2*) and in 100 patients with pseudoxanthoma elasticum (*chapter 3*) a follow-up study was performed to investigate the association between these connective tissue disorders and symptomatic intracranial aneurysms.

In **chapter 4** the biochemical properties of type III collagen are discussed, and the possible relationship between type III collagen deficiency and intracranial aneurysms is reviewed. Protein analysis was performed of skin fibroblasts from 41 consecutively admitted patients with intracranial aneurysms, and 41 healthy volunteers to investigate if the production of type III collagen is lower in patients (*chapter 5*). Subsequently, the type III collagen gene in the group of 41 consecutive patients with intracranial aneurysms was analysed for mutations or other defects e.g. null alleles. (*chapter 6*).

In **chapter 7** a family is described of which three members had an intracranial aneurysm. Protein and DNA analysis was performed for the presence of a type III collagen deficiency, and subsequently the underlying cause of the deficiency was investigated.

References

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The pathogenesis of intracranial aneurysms

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