Intracranial aneurysms and connective tissue disorders

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Type III collagen and intracranial aneurysms

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Type III collagen: biochemistry and genetics

Type III collagen deficiency is possibly related to the formation of intracranial aneurysms. At least 16 different types of collagen have been identified. The major fibrillar collagens are type I, II, and III. Type I is present in most connective tissues, type II primarily in cartilage, and type III is mainly found in skin, gut, placental membranes and is a major component of the blood vessel wall.1-3

A type III collagen molecule consists of three identical pro-\(\alpha1(III)\) chains produced by the rough endoplasmic reticulum of the cell. Each procollagen chain contains a strand of about 1000 residues long in an alpha(\(\alpha\))-helix, rich in glycine (every third residue) and proline, and two globular parts on the amino(N)- and carboxyl(C)-terminal ends. The pro-collagen chains associate at the C-terminal end, prior to spontaneous triple helix formation.3,4 The stability of the triple helix depends on the locking effect of proline-hydroxyproline residues and on the hydrogen bonding by the hydroxyl group of hydroxyproline. Subsequently the procollagen undergoes post-translational modifications. The N- and C-propeptides are cleaved by specific endopeptidases. The collagen then spontaneously assembles into fibrils.2,3

Type III collagen deficiency can result from a variety of mechanisms, e.g. genomic deletion of one of the type III collagen alleles,5 point mutations leading to abnormal splicing (i.e. exon skipping and insertions),4,6 substitutions in the \(\alpha\)-helix (i.e. a point mutation replacing an amino acid residue often glycine),2,4,6 or a dysfunction during the post-translational modifications.3

Relationship between type III collagen deficiency and intracranial aneurysms?

Type III collagen is an attractive candidate to play an important role in the pathogenesis of intracranial aneurysms. It is very firm and responsible for the tensile strength of the arteries, especially when the strain on the vessel wall becomes high.7-9 Ehlers Danlos Syndrome (EDS) type IV is a connective tissue disease which is characterized by a genetically determined defect of type III collagen due to a decreased type III procollagen production or a production of structurally altered type III collagen.2 Patients with this syndrome have an
increased propensity for carotid-cavernous fistulas, arterial dissections, and intracranial aneurysms. The vascular fragility in EDS type IV is a feared problem in surgery and arteriography.

Several studies have demonstrated a relationship between type III collagen deficiency or unstable type III collagen and intracranial aneurysms. Neil-Dwyer et al. obtained skin and arterial fibroblasts from 17 patients undergoing surgery for ruptured intracranial aneurysms and from 6 age- and sex-matched controls. The type III / type I collagen ratios were measured by carboxymethyl cellulose chromatography (CMC) or gel scanner, two different methods of collagen determination. CMC was performed in 11 patients and gel scanning in another 11 patients. In 11 patients (64%) a type III collagen deficiency was found while all of the 6 controls had normal type III / type I collagen ratios. Östergaard et al. used post-mortem samples of the middle cerebral artery of 14 patients who died of a ruptured intracranial aneurysm and from a control group of 14 patients who died of unrelated causes. Through electrophoresis and densitometry a type III collagen deficiency was detected in 43% (6 patients) of the ruptured aneurysm group. This study suffers from a selection bias as only deceased patients were included. There was a fairly large difference between type III / type I collagen ratios from the middle cerebral artery and the brachial artery in several patients. An explanation is that Östergaard et al. used biopsies of the whole artery wall resulting in a mixture of endothelial and medial smooth muscle cells. This may influence the type III / type I collagen ratio since there is a variation in collagen synthesis in endothelial and smooth-muscle cells as was shown in cultures from pig aortas. Although these studies were small, they indicate a relation between type III collagen deficiency and intracranial aneurysms.

However, in another small study Leblanc et al., using gel electrophoresis, showed no type III collagen deficiency in skin fibroblasts of five female patients with intracranial aneurysms who all had a positive family history for intracranial aneurysms. Majamaa et al. using gel electrophoresis and densitometry, could not demonstrate type III collagen deficiency in 11 patients with intracranial aneurysms, but found a production of unstable type III collagen in skin fibroblasts of 2 patients. In this study six patients (55%) had a relative with an intracranial aneurysm including the 2 patients with unstable type III collagen production.
It is not clear whether the type III collagen gene is involved in the demonstrated type III collagen deficiency.\textsuperscript{21,22} Kuivaniemi et al. performed DNA sequence analysis of type III collagen cDNA in 40 patients with intracranial aneurysms and found no mutations in the part of the gene encoding the $\alpha$-helix and the telo-peptides.\textsuperscript{28} Therefore it is not likely that this part of the gene is often involved in the formation of intracranial aneurysms. However, the 3' end of the gene, encoding the C-pro-peptide, has not been analyzed in patients with intracranial aneurysms. The globular part of the C-propeptide is essential in formation of the triple helix of all fibrillar collagens.\textsuperscript{3,4} A mutation in the C-terminal part may theoretically lead to a failure of association of the triple helix with an intracellular breakdown of the mutated pro$\alpha$1 chain or it may lead to an abnormal association with all three $\alpha$1 chains being destroyed.\textsuperscript{5}

Mutations in the C-propeptide of type III collagen, defects in gene regulation or in collagen processing may cause a deficiency of type III collagen.

References


