

## Spontaneous Cervical Artery Dissection From Risk Factors Toward Pathogenesis

Tobias Brandt, MD; Caspar Grond-Ginsbach, PhD

The pathogenesis of a cervical artery dissection (CAD) remains unknown in most cases.<sup>1,2</sup> Dissections are usually classified as either traumatic or spontaneous.<sup>3</sup> However, mechanical trauma did not appear to be an important and frequent cause for the development of CAD, neither in clinical nor in histopathological studies. Chiropractic maneuver, for instance, was repeatedly discussed as a risk factor for CAD, but its pathogenetic effect could be proven only in a minority of cases.<sup>4</sup> Signs of mechanical damage could not be observed in the majority of preparations in a histopathological study of 50 dissected carotid arteries.<sup>5</sup> As a result, factors other than mechanical were increasingly taken into consideration in the pathogenesis of cervical artery dissections.

Several constitutional risk factors have been associated with nontraumatic, spontaneous cervical artery dissection (sCAD).

- Hereditary connective tissue disorders, in particular the vascular Ehlers-Danlos syndrome (EDS), are known to be a risk factor for spontaneous dissections. Vascular EDS is an autosomal dominant disorder. Most patients carry mutations in the gene that encodes the pro- $\alpha$ 1(III) collagen.<sup>6</sup> Also, other subtypes of EDS (hypermobility and classic forms) are known to predispose for sCAD. Collagen defects, mostly mutations in the pro- $\alpha$ 1(V) and pro- $\alpha$ 2(V) encoding genes, have been identified as the pathogenetic cause in the majority of patients with classic EDS.<sup>7</sup> The molecular defect in the hypermobility subtype of EDS is not yet known<sup>8</sup>.
- The morphology of connective tissue elements was found to be aberrant in the majority of skin biopsies from patients with sCAD lacking clinical stigmata of a known connective tissue disorder,<sup>9,10</sup> pointing to a molecular defect in the biosynthesis of the extracellular matrix (ECM). Comparable abnormalities have not been found in skin biopsies from healthy control subjects. This finding suggests that patients with sCAD suffer from an unknown connective tissue disorder that predisposes for structural weakness of the vessel wall and therefore increases their risk for dissections. Recent electron microscopic investigation of skin biopsies from healthy relatives of patients give strong evidence for familial occurrence of connective tissue alter-

From the Department of Neurology (T.B., C.G-G.), University of Heidelberg, and the Department of Neurological Rehabilitation (T.B.), Schmieder-Kliniken Heidelberg, Germany.

Correspondence to Dr T. Brandt, Department of Neurology, University of Heidelberg, Im Neuenheimer Feld 400, D-69120 Heidelberg, Germany. E-mail Tobias\_Brandt@med.uni-heidelberg.de

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ations. Furthermore, they might follow a dominant autosomal pattern of inheritance, at least in the few families studied thus far<sup>11</sup>.

sCAD has been associated with fibromuscular dysplasia, a rare, nonatherosclerotic, noninflammatory disease of the intermediate-sized arteries, which mainly affects the carotid and renal arteries<sup>12</sup>.

Only a minority of the patients with sCAD have a family history of dissections—those few patients were found to have an increased risk (more than 5-fold) of recurrent dissection<sup>13</sup>.

The assumption of an autosomal dominant connective tissue aberration as predisposition for a disorder that is rarely familial seems to be a paradox. Probably the penetrance of the genetic disposition is low, which means that the connective tissue aberration is by far not a sufficient cause for sCAD. Other factors, both constitutional and/or environmental, are needed to explain why only some people at risk develop sCAD and others do not.

- An infection in the few weeks prior to a symptomatic dissection was found to be an independent risk factor for sCAD,<sup>14</sup> and it seems reasonable to correlate the observed seasonal pattern in the incidence of sCAD<sup>15</sup> to the seasonal variation in infection diseases.
- Mild hyperhomocysteinemia was recently found to represent a risk factor for sCAD in a study of 26 patients and 30 healthy control subjects.<sup>16</sup> Homozygous carriers of the C677T mutation of the methylenetetrahydrofolate reductase (*MTHFR*) gene encoding the thermolabile form of the enzyme are known to have mild to moderate hyperhomocysteinemia. However, the observed association of sCAD with *MTHFR TT* genotype was not considered significant in that study.

In this issue of *Stroke*, Pezzini and coworkers not only confirm the association between sCAD and mild hyperhomocysteinemia, but also demonstrate a significant association with the *MTHFR TT* genotype.<sup>17</sup> About 10% of the normal population was homozygous for the thermolabile variant of *MTHFR*. Among 51 patients with sCAD, the number of *MTHFR TT* carriers was found to be 16 (31%), as can be deduced from the combined data of both studies. Not only the concentration but also the standard deviation of plasma homocysteine concentration is elevated in carriers of the *MTHFR TT* genotype. Homozygous carriers have partially lost the ability to keep their plasma homocysteine levels within a narrow range. Chronic and mild as well as acute and dramatic elevation of the homocysteine level might represent additional risk factors for sCAD in homozygous carriers.

Because moderately elevated plasma homocysteine levels have been established in some studies as an independent risk factor for atherosclerosis and its complications, including cerebrovascular disease,<sup>18</sup> the (weak) association between the *MTHFR TT* genotype and sCAD is particularly interesting. However, the relationship between sCAD and hyperhomocysteinemia seems to be complex, since sCAD is not considered an atherosclerotic disease. Moreover, in the group of atherothrombotic stroke patients, no association with the thermolabile encoding genotype could be established by Pezzini and coworkers.

An arterial dissection is probably the endpoint of a complex and possibly heterogeneous group of vasculopathies developing under the influence of various genetic and environmental factors. Frequent conditions like a recent infection or homozygosity for the thermolabile form of *MTHFR* cannot be sufficient causes for the development of sCAD. Ultrastructural ECM alterations, on the other hand, are rare and have only been observed in skin biopsies from patients with some well-defined disorders, such as EDS<sup>19</sup> or sCAD.<sup>9,10</sup> The association of sCAD with inherited ultrastructural connective aberrations in the majority of patients on one hand and the rare occurrence of familial dissections ( $\ll$  5%) on the other hand suggests that other factors exist that must interfere before carriers of an inherited connective tissue disorder develop a cervical artery dissection. Mild hyperhomocysteinemia and its genetic determinants might be considered additional risk factors. It is conceivable that moderate hyperhomocysteinemia plays a role in the pathogenesis of only some sCAD subtypes. Studying families with an inherited ECM disorder might be helpful for the investigation of the impact of mild hyperhomocysteine on sCAD. The ultrastructural connective tissue phenotype is now being studied as an inherited marker that enables the investigation of families of an sCAD patient by genetic linkage analysis. However, it is unknown why some carriers of the ECM phenotype develop sCAD and why others do not. It will be of interest to consider the C677T mutation as an additional pathogenetic factor in such families.

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