The Association of Connective Tissue Disorders with Cervical Artery Dissections

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Abstract: A predisposing weakness of the vessel wall has been assumed in patients with spontaneous cervical artery dissections (sCAD). Skin biopsies from many patients with sCAD show mild connective tissue alterations. However, their assessment depends on an invasive and highly specialized technique. Clinical signs of connective tissue disease are absent in the majority of CAD patients.

In this review we document that only very few CAD patients are affected by known inherited connective tissue disorders like Ehlers-Danlos syndrome, Marfan syndrome or Osteogenesis Imperfecta. In a second part of this review we discuss the possible role of unrecognized or unknown forms of connective tissue disorders in the etiology of CAD.

INTRODUCTION

An arterial dissection is a tear within the wall of an artery. The flow of blood in between the layers of the torn blood vessel may cause the artery to narrow and even close off entirely. Once considered uncommon, dissections of the carotid or vertebral arteries are now recognized as the major cause of ischemic stroke in young patients (< 50 years). The diagnosis of a cervical artery dissection (CAD) is confirmed by the visualization of a mural hematoma on MRI [1].

Dissections of brain supplying arteries affect all age groups, including children, but there is a distinct peak in the fifth decade of life. There are more male than female patients. At the time of their dissection women are on average younger than men [2]. CAD may occur simultaneously in two or more vessels. The frequent occurrence of simultaneous dissections (about 13% in CAD series with a population-based recruitment [3]) and the fairly high rate of recurrent dissection within the first four to six weeks may be related to a transient arteriopathy [1, 4]. Asymptomatic recurrent dissections were observed in patients during diagnostic follow-up studies, but the incidence of asymptomatic CAD is unknown. The incidence of symptomatic CAD is about 3/100,000 a year [1, 3]. The mean age of occurrence of CAD being 44-46 years [4, 19], and the reported mortality rate being low [3,19], we estimate that the prevalence of CAD is approximately 1/1000 (assuming roughly that the mean survival after CAD is approximately 30 years).

Only one study has systematically searched for the presence of a family history of dissection and found that among 200 consecutive CAD patients, 6 (3%) had a family history of CAD and 4 had a family history of renal or aortic dissection [5]. This may be an overestimation, due to the recruitment bias in this tertiary referral series and the fact that all cases of a same family were included. On the other hand, a family history of CAD is likely to be underreported both because CAD may occur asymptomatically, and because CAD may have been unrecognised in parents of CAD patients, given the limited number of non-invasive diagnostic tools that were available before magnetic resonance imaging became available. Despite the absence of reliable data on the heritability of CAD, an inherited weakness of the vessel wall predisposing to CAD was repeatedly discussed, given the apparent spontaneity of many dissections and their occurrence in young persons without vascular risk factors [6]. Case reports about CAD patients with associated inherited connective tissue defects (alpha-1-antitrypsin deficiency, Ehlers-Danlos syndrome and Marfan syndrome [7-9]) nourished the assumption of an underlying connective tissue disease in patients with CAD.

The finding of mild alterations in the morphology of the connective tissue in skin biopsies from many CAD patients [10, 11, 12] confirmed that CAD patients carry some connective tissue abnormality. However, the cause of the electron microscopic alterations in the patients' dermal connective tissue is not yet characterized. Patients with clinical signs of a known connective tissue disease were excluded from the series that was studied by electron microscopy. Moreover, CAD patients with clinical signs of connective tissue disease are rare [13]. It is therefore unclear, whether CAD patients with dermal connective tissue alterations suffer from an unknown connective tissue disorder, or whether they suffer from a mild form of known disorders, as sometimes suggested [14].

The first part of this review analyzes the possible association between CAD and three well known connective tissue disorders. In the second part of this review we will discuss the hypothesis that unrecognized or other yet unknown connective tissue disorders play a role in the etiology of CAD.

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CAD IN PATIENTS WITH KNOWN INHERITED CONNECTIVE TISSUE DISORDERS

Ehlers Danlos Syndrome

Ehlers-Danlos syndrome (EDS) is a clinically and genetically heterogeneous connective tissue disorder affecting as many as 1/10,000 individuals. In its most common form EDS is characterized by hyperextensibility of the skin, hypermobility of joints, and tissue fragility [15]. The recognition of frequent ultrastructural abnormalities of collagen fibrils in EDS patients led to the concept that EDS is a disorder of collagen fibrils. Following the identification of specific mutations in the genes encoding collagen types I, III, and V, as well as several collagen processing enzymes, EDS is classified in several distinct clinical subtypes. The vascular type of EDS (vEDS), also called EDS type IV, is the most severe form of EDS. It accounts for less than 4% of all EDS patients (e.g. its prevalence is < 1/200,000). Patients with vEDS are significantly less frequent than patients who develop CAD during their life (about 1/1000). Therefore patients with vEDS must be rare in cohorts of CAD patients. Indeed the following two studies indicate that only a minority of vEDS patients develop dissections of the brain supplying arteries [16, 17].

Pepin *et al*. [16] studied 220 index patients with biochemically confirmed vEDS and 199 affected relatives (a subset of these patients was analyzed before [17]). In the entire cohort (419 subjects), 43 patients had arterial complications of the central nervous system between 17 and 65 years (mean age: 32.8 years). Eight carotid artery dissections (1.9%) were observed. Another series of 31 patients with a clinical diagnosis of vEDS (15 men, 16 women) were studied in a department of vascular surgery [18]. 24 of these patients suffered from 132 vascular complications, among them eight carotid and two vertebral artery dissections. The authors do not mention in how many patients these 10 cervical artery dissections occurred.

Patients with vEDS were only rarely observed in cohorts of CAD patients. In a large series of 696 patients with CAD from France and Switzerland six patients showed a family history of connective tissue disorder. However, their diagnosis was not specified [2]. In a detailed analysis of a subset of these patients published elsewhere one patient with ”known Ehlers Danlos syndrome” was found [19]. Among 459 CAD patients from a multicenter French study [20] no patient with vEDS was reported. In a German series of 126 CAD patients [21], the authors did not observe a single a patient with a known connective tissue disorder.

There are a few case reports of vEDS patients with CAD. Schievink *et al.* [8] presented a 16 year old girl with clinical vEDS and a dissection of the right internal carotid artery. Another report [22] described a 34 year old patient who experienced a simultaneous dissection of both internal carotid arteries and both vertebral arteries. A skin biopsy from the patient showed ultrastructural connective tissue alterations. The mother of the patient had also suffered a cervical artery dissection [22]. However, the microscopic diagnosis of vEDS in this study was not confirmed by biochemical or molecular methods. Martin *et al*. [23] found a COL3A1 glycine substitution in two cousins who both suffered a dissection of the internal carotid artery at ages of 18 and 19 years. These two patients did neither show typical clinical signs of vEDS syndrome, nor aberrations of their connective tissue morphology.

Because of the very low prevalence of vEDS, CAD patients with vEDS are expected to be rare. Observations from a few large clinical series of CAD patients confirm this expectation, although clinical criteria of vEDS were not systematically searched for in these series. Thus, current data suggest that vEDS is present in less than 1 percent of CAD patients.

Marfan Syndrome

Marfan syndrome (MS) is an autosomal-dominant disorder, caused in the majority of cases by mutations in the FBN1 gene, and in a minority of cases (10%) by mutations in TGFBR2 or TGFBR3 [24]. The disease has a variable clinical manifestation, involving the skeletal, cardiovascular and ocular systems. Dissections of the aorta are a main symptom of the Marfan syndrome. Marfan syndrome occurs in 1/10,000 to 1/15,000 newborns. In a retrospective study from the United States, including 513 patients with a clinical diagnosis of Marfan syndrome [25], 18 patients had a neurovascular complication, but none of them suffered sCAD. In a Dutch series of 135 patients [26] classified as having Marfan syndrome, none of the patients was found to suffer from intracranial aneurysms and it is to be expected that CAD cases would have been reported if there had been any. No case of CAD was reported either in a recent very large series of 1013 MFS patients, although the clinical description of central nervous system complications is not given in detail [27].

These studies suggest that CAD is not associated with Marfan syndrome. However, some case studies presented Marfan syndrome patients with CAD [9, 28, 29]. In large CAD series, three patients with „documented Marfan syndrome“ were also found among 459 patients with CAD [20] and one Marfan patient among 195 patients with vertebral artery dissection [19]. It is unclear how the diagnosis of Marfan syndrome was made in these few reported cases. Besides it is sometimes difficult to be sure that the CAD was not an extension of a concomitant or prior proximal aortic dissection. Overall, these sparse observations suggest that Marfan syndrome is extremely rare among patients with CAD. The absence of CAD cases in several large series of well phenotyped patients with Marfan syndrome even raises the question whether CAD can really be considered as a potential complication of Marfan syndrome.

Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) is a genetic disorder of low bone mass, increased bone fragility and other

connective tissue manifestations. It affects between 1/10,000 and 1/20,000 newborns. OI patients are usually classified into four clinical subtypes [30]. Recently three additional subgroups who present clearly distinct features have been proposed [31]. Molecular analysis of a patient with a spontaneous multivessel CAD and minor signs of OI revealed a substitution of alanine for glycine (G13A) in the alpha 1(I) chain of type I collagen [32]. A few other patients with OI and CAD were presented in case studies [33, 34]. Another patient with OI was found in a small prospective series of 43 patients with CAD [13]. There are no published data on the prevalence of CAD in cohorts of patients with OI. Thus, the few isolated observations of CAD in patients with OI are currently insufficient to suggest a consistent association.

Summary

Vascular EDS, Marfan syndrome and OI are rare diseases. Reports from series of patients with these monogenic connective tissue disorders suggest that CAD is a possible but relatively rare complication of vEDS, while the occurrence of CAD in patients with Marfan syndrome or OI seems exceptional. Data from prospective series looking specifically for neurovascular complications of these connective tissue disorders over several years are lacking.

Studies on large cohorts of CAD patients also suggest that known inherited connective tissue disorders are rare in CAD patients ($\leq$1%). These studies were however not designed specifically to describe the association of CAD with heritable connective tissue disorder. Therefore, the few CAD patients who had a heritable connective tissue disorder are not described in detail. In particular, it is unclear whether the diagnosis of vEDS, Marfan or OI was biologically confirmed, or whether it relied only on clinical criteria. Besides, except for one series of 43 CAD patients, none of these cohorts systematically screened all CAD patients for clinical criteria of connective tissue disorders.

Although CAD is only rarely caused by monogenic connective tissue disorders, it is important to screen CAD patients for suggestive clinical signs or a positive family history, especially of vEDS, and if there is a strong clinical suspicion, the patient should be directed to a geneticist for further diagnostic tests. Indeed, if the diagnosis be confirmed, preventive measures are indicated that can reduce the incidence of severe complications and genetic counselling must be proposed.

ON THE POSSIBLE ROLE OF UNRECOGNIZED OR UNKNOWN CONNECTIVE TISSUE DISORDERS IN THE ETIOLOGY OF CAD

Disease causing mutations in patients with a known heritable connective tissue disorder might have quite variable phenotypes within the same family. A G499D substitution in the alpha1 chain of type III procollagen (COL3A1) was found in a 49 year old patient with the acrogeric form of EDS who died from massive pulmonary emboli and acute myocardial infarction. His son carried the same mutation but was clinically normal at 15 years of age [35]. Highly variable phenotypes of COL1A1 mutations within a family were also observed [36,37]. Extreme intrafamilial variability was described particularly in kindreds with Marfan syndrome [38]. These findings suggest that patients with typical disease mutations for these disorders might show a fully normal phenotype. Perhaps some of these carriers develop CAD as the only symptom of their disorder [see also 23]. It is unknown whether asymptomatic carriers of disease-causing mutations in candidate genes for known inherited connective tissue disorders are rare or common. However, mutations in known candidate genes for these disorders were not found in several series of CAD patients [39-43].

A broad spectrum of further connective tissue phenotypes with arterial findings has been described. Some authors for instance have suggested an association of chronic fatigue syndrome with extensible skin and stiff arteries [44]. In a family with arterial tortuosity syndrome all affected patients showed signs of EDS (soft skin with abundant subcutaneous tissue, joint laxity and hernias) [45], but a distinct clinical and molecular entity was subsequently diagnosed, with a causal mutation in the GLUT 10 gene [46]. Recently the Loeys-Dietz syndrome was defined as a new hereditary connective tissue syndrome with mutations in the TGF-beta receptor (TGFBR1 and TGFBR2) [47]. In addition to hypertelorism, bifid uvula or cleft palate, and generalized arterial tortuosity, patients with Loeys-Dietz syndrome type II have clinical signs suggestive of vEDS, including joint laxity, easy bruising, translucent skin with easily visible veins, arterial aneurysms and dissections end catastrophic complications of pregnancy, including rupture of the gravid uterus. Some of these newly described connective tissue disorders maybe associated with CAD. Interestingly, among a series of 90 subjects with Loeys-Dietz syndrome from 52 families, 9 (10%) had aneurysms on head or neck arterial branches. Whether the aneurysms on neck branches correspond to CAD is not mentioned in the article [47], but to our knowledge CAD is a major, cause of aneurysm in this location.

Finally, CAD may be associated with other, yet unknown connective tissue diseases. Recently, a systematic search for mild connective tissue signs among 43 patients with CAD (and 43 consecutive patients of similar age with ischemic stroke of other etiology as controls), performed by specialists, did not reveal any association between CAD and a composite score of diverse mild connective tissue signs [13]. Although such a heterogeneous composite score may not be very discriminating and the size of the series is small, it suggests that most CAD patients have no clinically obvious signs of connective tissue disorder. This does not however exclude that CAD patients may be affected with a mild form of connective tissue disease of which CAD would be the only clinical expression. The finding of mild alterations in the dermal connective tissue from patients with CAD [10, 11, 12] and from patients with

intracranial aneurysms [48] seems to strengthen the idea that unknown connective tissue alterations might be associated with these two closely related arterial diseases. In these electron microscopic investigations only patients without obvious clinical signs of connective tissue disease were included. Some other studies with similar results, however, also included patients with an EDS like appearance [14]. These dermal connective tissue alterations could not be related to mutations in candidate genes for known connective tissue disorders [49]. There are however strong arguments for a familial transmission of this phenotype, possibly following an autosomal dominant pattern [50, 51]. Although not significant and shown in a single family until now, a suggestive candidate locus on chromosome 15q24 was recently identified [51].

Summary

Clinical signs of connective tissue disease, even mild signs, are rare in CAD patients. This does not exclude that a few CAD patients may be affected with mild, otherwise unrecognized forms of known connective tissue diseases. Furthermore, CAD may be associated with other, yet unknown, heritable connective tissue diseases, as suggested by the electron microscopic findings in skin biopsies from CAD patients who do not appear to have any other obvious clinical sign of connective tissue involvement. Until now, systematic screens for mutations in major genes involved in the connective tissue homeostasis have been negative. It is to be expected that in a near future, large multicentre collections of CAD patients will be used to perform genome wide association studies, possibly leading to the identification of unsuspected genetic susceptibility factors for CAD. If some of these happen to be involved in the structure and function of connective tissue elements in the arterial wall, it would improve our understanding of the relationship between CAD and connective tissue disorders. Further linkage analyses on several large families with inherited dermal connective tissue alterations could also be of great help by identifying genetic loci that cosegregate with the dermal connective tissue phenotype.

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