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REVIEW ARTICLE

CAROTID ARTERY DISSECTION AND CONNECTIVE TISSUE DISORDERS: A REVIEW OF KNOWN GENE/PROTEIN MUTATION FINDINGS

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Summary

In this review, we comprehensively analyze the existing literature on the association between connective tissue disorders (CTDs) and carotid artery dissection (CAD), focusing on proven gene and protein mutations. By synthesizing evidence from various studies, we aim to provide a clearer understanding of the underlying mechanisms and potential genetic factors involved in the development of this condition. CAD, a leading cause of stroke in young adults, has been linked to CTDs such as Ehlers-Danlos syndrome, Marfan syndrome, and Loeys-Dietz syndrome, all of which involve genetic mutations that weaken vascular connective tissues. The review reveals that mutations in genes like *COL3A1*, *FBN1*, *TGFBR1* and *TGFBR2* play a crucial role in the integrity of arterial wall. It discusses the significance of these findings in identifying individuals at risk and developing targeted treatment strategies. Moreover, the article highlights the significance of identifying mild connective tissue abnormalities in patients with spontaneous CAD and advocates for more extensive genetic studies to enhance our understanding of CAD's genetic architecture. By identification of unique protein expression profiles, future research may lead to improved diagnostic and therapeutic approaches for CAD linked to CTDs.

Key words: carotid artery dissection; stroke in adults; connective tissue disorders; gene mutation; protein mutation

Introduction

Carotid artery dissection (CAD) is defined as a hematoma in the wall of the carotid artery and represents a leading cause of stroke in the young population. Recent studies have highlighted the potential connection between

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carotid artery dissection and connective tissue disorders (CTD), leading to a growing interest in this field of research. Understanding the connection between connective tissue disorders and carotid artery dissection is crucial for identifying individuals at risk and developing targeted treatment and management strategies.

The prevalence of carotid artery dissection has been estimated to be between 2.6 and 2.9 per 100,000 individuals per year, with a higher incidence in younger age groups (below 45 years) and a slight male predominance (1). This tear results in the formation of a blood clot or hematoma that can partially or completely block the flow of blood to the brain (2). Clinically, CAD is usually presents with "local" symptoms and signs partly due to compression of adjacent structures, including headache, cervical pain, Horner syndrome, and cranial nerve palsy. In up to three-quarters of patients in published series, CAD is complicated by cerebral ischemia or, rarely, retinal or spinal cord ischemia, typically occurring several hours or days after the onset of local symptoms (3). The etiology of over 50% of the CAD cases is spontaneous, with prior trauma is identified in approximately 40% of cases. Up to 90 % traumatic events are mild or trivial insults such as neck movements or minor injuries (4). The prevailing hypothesis regarding the pathogenesis of spontaneous CAD (sCAD) is that the underlying constitutional vessel wall weakness in patients with sCAD is genetically determined, and that environmental factors could act as triggers (5).

Connective tissue disorders and proven associated gene mutations

Connective tissue disorders are acknowledged as a significant risk factor for carotid artery dissection (6). The prevalence of mixed CTD has been estimated to be as high as 1.9 per 100,000 individuals per year (7). These disorders, which include Marfan syndrome, Ehlers-Danlos syndrome, and fibromuscular dysplasia, are characterized by genetic mutations that affect the strength and integrity of the vascular system's connective tissues. The weakened arterial walls are more susceptible to tearing under stress or even spontaneously, making individuals with these conditions more prone to carotid artery dissections. A comprehensive understanding of the relationship between connective tissue disorders and vascular integrity has been pivotal in identifying individuals at risk and implementing preventative strategies to reduce the likelihood of carotid artery dissection and its potentially life-threatening complications. Below is a concise overview of each syndrome, along with the associated gene or protein mutation.

Ehlers-Danlos syndrome type IV (the vascular type of Ehlers-Danlos syndrome) is one of the hereditary connective tissue disorders associated with an increased risk of CAD with a prevalence of 1/50,000-1/200,000 (8). This syndrome is characterized by a defect in the production of type III collagen, which results in the weakening of blood vessel walls. Patients with this syndrome may present with a variety of vascular complications, including arterial aneurysms and dissections. Ehlers-Danlos syndrome type IV is caused by mutations in the *COL3A1* gene, which codes for type III procollagen (9).

Another disease caused by a connective tissue defect is Marfan syndrome, which has a prevalence of 6.5 per 100,000 individuals (10). It is an autosomal dominant disease in which a single defect in the *FBN1* gene on chromosome 15, which codes for the connective tissue protein fibrillin, has been identified (11). Abnormalities in this protein result in a wide range of clinical manifestations, the most prevalent being cardiovascular manifestations, including aortic dilatation and dissections.

Loeys-Dietz syndrome (LDS), is rare a genetic disorder (25% autosomal dominant, 75 % de novo) with prevalence of 1/ 100,000 to 1/200,000, that affects the body's connective tissue. It is characterized by a wide spectrum of skeletal, craniofacial, cutaneous, and vascular findings; the latter comprising cerebral, thoracic, and abdominal arterial aneurysms and/or dissections and severe arterial tortuosity. Diagnosis involves clinical features or identification of specific pathogenic variants in genes like *SMAD2*, *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1*, or *TGFBR2*. The underlying genetic mutations, particularly in the *TGFBR1* and *TGFBR2* genes, disrupt the normal function of the transforming growth factor-beta signaling pathway, leading to the structural weakness of arterial walls (12). LDS has been associated with an elevated risk of arterial dissection and aneurysm formation (13).

In addition to Ehlers-Danlos syndrome type IV, LDS and Marfan syndrome, fibromuscular dysplasia (FMD) has also been identified as a potential risk factor for of CAD. The prevalence of FMD is estimated to be 12 per 100,000 (14). This non-inflammatory, non-atherosclerotic arterial disease, predominantly affecting women,

is characterized by abnormal cell growth in the arterial wall, leading to stenosis, aneurysm formation, and dissection. The result of a 202 genome-wide association meta-analysis, including six studies (a total of 1,556 FMD cases and 7,100 controls) showed four strongly associated loci *PHACTR1*, *LRP1*, *ATP2B1* and *LIMA1*. These target genes are widely involved in mechanisms related to the actin cytoskeleton and intracellular calcium homeostasis, which is crucial to vascular contraction. There is evidence of significant genetic overlap between FMD and more common cardiovascular diseases and common traits include blood pressure, migraine, intracranial aneurysm and coronary artery disease (15). Research suggests that the abnormal growth of cells in the arterial wall may contribute to the weakening of the vessel wall, making it more prone to dissection.

Osteogenesis imperfecta (OI) is another rare connective tissue disorder, whose main clinical manifestations include excessive bone fragility, blue sclerae, and hearing loss. It can be associated with an increased risk of arterial dissection especially with multiple spontaneous arterial dissection (16). Osteogenesis imperfecta is chiefly caused by mutations in the *COL1A1* and *COL1A2* genes, which encode type I procollagen (17).

Current research of carotid artery dissection and systemic disorders

The above evidence demonstrates that connective tissue disorders play a significant role in the development and progression of carotid artery dissection. Many of these disorders have genes that are responsible for the production of defective proteins that affect the structure of the vessel walls, thereby reducing their strength and flexibility.

While the presence of collagen vascular disorders that meet diagnostic and genetic criteria is rare in CADs (1–5% of spontaneous CADs), milder connective tissue abnormalities such as joint hypermobility, multiple dislocations, and poor wound healing are common in patients with spontaneous CAD (50–96%). Patients with subclinically increased vascular tortuosity or enlarged aortic root diameter also have an elevated risk for developing CAD. Therefore, it is likely that most cases of so-called spontaneous CAD occur within the context of systemic yet not clearly defined mild connective tissue disorders (5).

In 2009, a systematic review analyzed 15 studies dealing with the genetics of CAD, two studies reported associations with polymorphisms in *ICAM-1* and *COL3A1*, three studies reported an association with the *MTHFR 677TT* genotype. The *MTHFR 677TT* genotype was not confirmed in three other studies but was associated with elevated homocysteine levels. Elevated homocysteine levels could contribute to CAD by endothelial damage or by influencing the elastic properties of the arterial wall. The disadvantage of the study was the small number of patients and thus the insufficient strength of the evidence, so the conclusion of the meta-analysis was that progress in revealing the genetics of CAD will require the collection of DNA samples from large multicenter series (18).

The ongoing CADISP (Cervical Artery Dissection and Ischemic Stroke Patients) project, led by a multinational European network, aims to perform a novel genetic association analysis using genome-wide and candidate gene approaches. To facilitate this, DNA will be collected from approximately 1100 patients diagnosed with cervical artery dissection and 2000 healthy individuals serving as controls. The CADISP project focuses on cervical artery dissections, which include both carotid and vertebral dissections. While the terms "carotid artery dissection" and "cervical artery dissection" are often used interchangeably, they refer to slightly different anatomical regions. Carotid artery dissection specifically involves a tear in the inner layers of the carotid artery. In contrast, cervical artery dissection is a broader term that encompasses dissections of both the carotid and vertebral arteries in the neck region. Although both conditions can lead to stroke, they may present different clinical manifestations. Comprehensive clinical, laboratory, diagnostic, therapeutic and outcome data will also be systematically collected from all participants based on predefined criteria and standardized definitions (19).

Partial results are available. Patients with carotid artery dissection were found to be older, predominantly male, and have a higher frequency of recent infection compared to those with vertebral artery dissection. Carotid dissections were also associated with more severe strokes and worse outcomes, although they were less common than vertebral dissections. Importantly, the study highlighted, that patients with carotid dissections had a shorter time to diagnosis and inpatient stay but a higher incidence of persistent neurologic deficits. The prognosis for patients with extracranial carotidal artery dissection was generally good, with low mortality rates and a majority of patients with normal neurological examinations, despite the impaired quality of life in many cases. However, intracranial carotid artery

dissection, was associated with a worse prognosis, with a significantly higher mortality rate compared to extracranial dissection (20).

A large study based on CADISP network samples from 2017 investigated the role of genetic factors by identifying copy number variants (CNVs) in samples from CAD patients and control subjects. The microarray data from 833 patients with CAD and 2040 controls were analyzed. Although rare gene CNVs were similarly prevalent in both groups, there were differences in the genetic content. CNVs in CAD patients were enriched in genes associated with muscle organ development and cell differentiation, suggesting a potential link with arterial development. In addition, CNVs affecting the development of the cardiovascular system were more frequent in patients with CAD, especially in patients with a family history of CAD compared to controls. These findings suggest that rare genetic imbalances related to the development of the cardiovascular system may contribute to the risk of CAD. However, further validation in independent study populations is necessary to confirm these results (21).

With the increasing development of tools for gene and protein analysis, knowledge in the area between CAD and CTD has deepened. The following text will gradually focus on spontaneous carotid dissection, carotid dissection with familial association, multiple carotid dissections and recurrent multiple carotid dissection.

Spontaneous carotid artery dissection (sCAD)

The sCAD group contains the majority of patients from the groups listed above. Two consecutive studies demonstrated an association between sCAD and structural abnormalities in the connective tissue at the ultrastructural level, often without other clinical signs of connective tissue disease. A 2005 study even revealed that similar connective tissue abnormalities were detected in some first-degree relatives. This suggests a possible genetic predisposition due to a defect in the extracellular matrix of the arterial wall. The identified dermal connective tissue irregularities could serve as a phenotypic marker for further genetic investigations in CAD patients and their extended families, potentially uncovering underlying molecular defects in the extracellular matrix (22, 23).

A review from 2009 confirmed the finding of mild connective tissue alterations in patients with sCAD, the vast majority without clinical signs of connective tissue disease, and very few CAD patients are affected by known hereditary connective tissue disorders such as Ehlers -Danlos syndrome, Marfan syndrome or Osteogenesis Imperfecta (24).

A study from 2010 with genetic linkage analysis leads to the identification of mutations in different CAD disease-causing genes involved in the biosynthesis of the extracellular matrix (*FBN1*, *COL3A1*), in transforming growth factor (*TGF*) beta signaling (*FBN1*, *TGFBR1*, *TGFBR2*) and in the SMC contractile system (*ACTA2*, *MYH11*). These findings support the hypothesis that genetic factors play a role in the development of sCAD, potentially involving defects in the extracellular matrix and signaling pathways (25).

A 2012 study of CAD showed an enrichment of genes involved in extracellular matrix organization (*COL5A2*, *COL3A1*, *SNTA1*), collagen fibril organization *COL5A2*, *COL3A1* and possibly for genes involved in transforming growth factor beta (TGF)-beta receptor signaling pathway (*COL3A1*, *DUPS22*). They conclude that rare genetic variants may contribute to the pathogenesis of CAD, particular in patients with a microscopic connective tissue phenotype (26).

Among clinical studies that did not focus on gene or protein analysis, a noteworthy clinical study highlighted the work on 84 patients with spontaneous dissection, which showed that connective tissue abnormalities are frequent in patients with sCAD. According to the study, 81 out of 84 patients in the sCAD group had at least one detectable sign of connective tissue abnormality. This indicates a high prevalence of such abnormalities in the sCAD patient population (27).

Spontaneous carotid artery dissection (sCAD) in families

However, familial CAD is extremely rare, with only a few reported cases. In these familial CAD cases, there is a high intrafamilial correlation between affected vessels and ages at the first dissection. Skin biopsies from some familial CAD patients have shown mild connective tissue alterations, but the significance of these findings is still unclear (23).

Pioneering work from 1991 expanded our understanding of familial CAD through genetic analysis. Families were identified where intracranial aneurysms and cervical artery dissections coexisted, suggesting a shared arteriopathy (28).

A study analyzed 7 families with 15 CAD patients. Among these, 11 patients underwent a skin biopsy, and the tissue was used to analyze the coding sequences of *COL3A1*, *COL5A1*, *COL5A2*, and part of *COL1A1*. A missense mutation in the *COL3A1* gene (leading to a *G157S* substitution in type III procollagen) was detected in both patients from one family. Additionally, two patients from another family carried a rare nonsynonymous coding polymorphism in *COL5A1* (D192N); one of them also had a rare variant in *COL5* (29).

A recent study analyzed patients from nine families through whole exome sequencing, focusing on 11 candidate genes associated with arterial connective tissue disorders. The study found non-benign single nucleotide variants in four families, impacting genes associated with arterial connective tissue disorders: *COL3A1* (Gly324Ser), *FBN1* (Arg2554Trp and Gly343Arg), *COL4A1* (Pro116Leu), and *TGFBR2* (Ala292Thr). These findings suggest genetic heterogeneity within familial CAD and underscore the role of rare genetic variants in its pathogenesis (30).

In summary, familial carotid artery dissection (CAD) is an uncommon condition with a strong genetic component, as evidenced by the presence of similar arterial issues and onset ages within affected families. Research has identified mutations in collagen-related genes, such as *COL3A1* and *COL5A1*, which are key to vascular integrity, and other genes like *COL4A1*, *FBN1*, and *TGFBR2*, associated with connective tissue disorders and arterial wall stability. These findings, including specific mutations like *COL3A1* Gly324Ser and *FBN1* Arg2554Trp, underline the genetic heterogeneity and the role of multiple genes in the pathogenesis of familial CAD (29, 30).

Multiple spontaneous carotid artery dissections

One of the earliest articles discussing multiple spontaneous carotid artery dissections in the same patients and their association with connective tissue disorders is a case report that highlights that spontaneous dissection of multiple cervical arteries is associated with a genetic mutation in the type I collagen chain (G13A substitution, analysis of the *COL1A1* gene). This finding emphasizes the role of genetic connective tissue disorders in multiple CAD and suggests that certain inherited collagen abnormalities may increase susceptibility to arterial dissection. This report highlights the importance of genetic screening for CAD (31).

A recent study hypothesized that patients with multiple arterial dissections in different vascular regions without manifesting of known connective tissue syndromes may still have mild connective tissue abnormalities. From a cohort of 322 patients with cervical artery dissection, four individuals with additional arterial dissections in other locations were analyzed. Three of these patients underwent dermal biopsy and their dermal connective tissue was analyzed by electron microscopy, while DNA was analyzed through whole-exome sequencing and copy number variation analysis for all four patients. The findings revealed that all three patients who underwent dermal biopsy had pathological collagen fibers. Additionally, two patients had CNVs disrupting genes linked to arterial connective tissue dysfunction (*COL3A1*, *COL5A2* in one patient, and *MYH11* in another), and a third patient had a missense substitution in the *COL5A2* gene. The study concludes that these morphological and genetic alterations are significant and that genetic testing should be recommended for patients after recurrent arterial dissections, even in the absence of obvious phenotypic signs of connective tissue disorders (32).

Recurrent multiple spontaneous carotid artery dissections

In a study of morphology of dermal connective tissue, it was demonstrated that 56% of patients (total 238) with monophasic CAD and even 67% with late recurrent dissections, exhibit connective tissue abnormalities. The study is notable for the length of follow-up (up to 8 years) and showed a real risk of long-term CAD recurrence 7.1% (33) versus 1% often reported in the literature (34).

In another study, a cutting-edge quantitative proteomic approach was used to analyze proteins obtained from skin biopsies and found that patients with recurrent sCAD exhibited significantly different expression levels of 25 proteins compared to the other groups. Thirteen of these differentially expressed proteins are crucial for the structural integrity

of connective tissue or are associated with connective tissue disorders, clustering into groups, desmosome-related proteins (*DSP*, *EVPL*, *JUP*, *CDH3*) and collagen/elastin cluster (*COL12A1*, *COL1A2*, *COL4A2*, *ELN*, *MFAP5*, *LAMB2*, *HSPG2*). These results suggest that the extracellular matrix protein signature specific to recurrent sCAD could potentially useful for identifying patients at risk and for developing treatment strategies. However, larger-scale validation is needed before this signature can be used in clinical practice (35).

Conclusion

The review highlights the already well-established association between specific gene mutations and CAD susceptibility, particularly in the presence of connective tissue disorders such as Ehlers-Danlos syndrome, Marfan syndrome, Loeys-Dietz syndrome, and fibromuscular dysplasia. These genetic associations underscore the importance of collagen type III (*COL3A1*), fibrillin (*FBN1*), and transforming growth factor beta receptor (*TGFBR1/2*) signaling pathways in arterial wall integrity and resilience. While the presence of recognized connective tissue disorders in patients with CAD remains relatively rare, milder connective tissue abnormalities are often observed, particularly in patients with multiple, recurrent or familial CAD. Promising tools of molecular genetics or quantitative proteomics, aimed at identifying a unique protein expression profile in patients with recurrent or multi-sCAD may reveal a pathological subproteome important for connective tissue integrity or associated with connective tissue disorders. Proteins found in the extracellular matrix, such as those in the desmosome cluster (*DSP*, *EVPL*, *JUP*, *CDH3*) and the collagen/elastin cluster (*COL12A1*, *COL1A2*, *COL4A2*, *ELN*, *MFAP5*, *LAMB2*, *HSPG2*), represent a potential avenue for identifying disease-related genes and for identifying of patients at higher risk. However, the necessity of larger-scale validation before clinical application reinforces the continued need for robust, large-scale genetic studies capable of providing the statistical power needed to fully elucidate the genetic architecture of CAD. CAD is therefore a multifactorial disease with a significant genetic predisposition, where the expression of pathological proteins plays a fundamental role in its pathogenesis and could also play a role in its diagnosis, prevention and therapeutic interventions.

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Conflict of Interest Statement

The authors state that there are no conflicts of interest regarding the publication of this article.

Adherence to Ethical Standards

Not applicable.

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