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A narrative review of pathophysiological mechanisms associated with cervical artery dissection

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Objective: *The purpose of this narrative review was to describe pathophysiological risk factors that have been reported in association with cervical artery dissection (CAD) and to discuss the strength of those associations.*

Data Sources: *MEDLINE, PubMed, Manual Alternative and Natural Therapy System (MANTIS), and CINAHL databases were searched for the years 1966 through September 2006. Additionally, the literature generated by the searches was culled for relevant citations incorporated within the articles.*

Results: *The search strategy generated a total of 130 distinct citations, of which 49 were determined to be relevant after applying the study's selection criteria. An additional 6 references were harvested from the reference lists of the included articles.*

Summary: *The most compelling pathophysiological risk factors have to do with connective tissue abnormalities, which may contribute to a weakening of the vascular wall making it more susceptible to tearing. However, the exact pathogenesis of CAD is uncertain, especially in cases that occur spontaneously, are related to trivial trauma, or occur in the absence of discernable risk factors.*
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KEY WORDS: dissection, artery, cervical, risk factor

Objectif : *Cette étude sommaire visait à décrire les facteurs de risque physiopathologique relevés en association à la dissection de l'artère cervicale (DAC) et de traiter de la force de ces associations.*

Sources de données : *Les banques de données MEDLINE, PubMed, Manual Alternative and Natural Therapy System (MANTIS) et CINAHL ont fait l'objet de recherches portant sur les années 1996 à 2006. De plus, la littérature obtenue dans le cadre de ces recherches a été étudiée en vue d'extraire des citations pertinentes, intégrées par la suite dans les articles.*

Résultats : *La stratégie de recherche a généré un total de 130 citations distinctes, dont 49 ont été jugées pertinentes selon les critères de sélection de l'étude. Six références supplémentaires ont été recueillies parmi les listes de références des articles inclus.*

Résumé : *Les facteurs de risque physiopathologique sont liés à des anomalies du tissu conjonctif et peuvent contribuer à fragiliser la paroi vasculaire, susceptible de se déchirer. Toutefois, la pathogénie exacte de la DAC demeure incertaine, en particulier dans les cas spontanés, liés à des traumas mineurs ou survenant sans facteurs de risque apparents.*
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MOTS CLÉS : dissection, artère, cervical, facteur de risque

Introduction

Cervical artery dissection (CAD) is an uncommon vascular wall condition affecting the vertebral and/or internal carotid arteries that typically involves a tear at some point in the artery's intimal lining and the formation of a flap, which allows blood to penetrate into the muscular portion

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of the vessel wall. Blood flowing between the layers of the torn blood vessel may cause the layers to separate from each other resulting in arterial narrowing or even complete obstruction of the lumen.[1,2] Accumulated blood develops into thrombus, which may produce emboli that travel distally to obstruct the progressively smaller vessels in the brain, resulting in stroke. CAD is reported to be the underlying cause of nearly 20% of ischemic strokes in patients under 45 years of age.[3] However, when considering the underlying cause of ischemic strokes in general, CAD only accounts for about 2% of the total.[4] The reported incidence of internal carotid artery (ICA) dissection is 2.6 to 2.9 per 100,000[4,5] and 1 to 1.5 per 100,000 for vertebral artery (VA) dissection.[6] Thus, the incidence of CAD is probably within the range of 3.6 to 4.4 per 100,000.

Most CADs occur spontaneously; absent any identifiable precipitating event.[7] However, it appears that the cervical arteries are susceptible to dissection in association with a variety of trivial neck movements, including cervical spine manipulation (CSM).[6] This association is confusing, because people normally encounter innumerable trivial events during their lifetime without ever experiencing dissection. Examples include backing up a car, coughing, vomiting, unusual sleeping positions, and rhythmic movement of the head and neck to music.[8,9] Slightly less that 10% of CADs have been reported as being associated with CSM.[7]

It has been suggested that an underlying arterial abnormality must be present in CAD patients, which predisposes them to dissection.[10–12] These patients tend to have a variety of risk factors more frequently than the unaffected population. However, assessing the contribution of individual risk factors is complicated, because many CADs occur in people with no detectible risk factors, who are in otherwise good health and who have not been exposed to trauma. Practitioners who utilize CSM should be aware of CAD risk factors in order to identify patients who may be susceptible to developing CAD following manipulation prior to treatment.

The purpose of this narrative review is to describe pathophysiological risk factors that have been reported as being associated with CAD and to discuss the strength of those associations. A recent systematic review by Rubinstein et al.[13] looked at case-control studies that have investigated CAD risk factors, including aortic root diameter > 34 mm, migraine headache, relative diameter change during the cardiac cycle of the common carotid artery, trivial trauma (in the form of neck manipulative therapy), hyperhomocysteinemia, recent infection, and alpha-1-antitrypsin. The authors reported that nearly all of them were influenced by a variety of shortcomings, such as information-bias, selection-bias, and confounding. They concluded that there was little evidence to support the presumed risk associated with these potential risk factors. Several new studies have been published since the date of the Rubinstein review (February 2005), which are included in the current review. In addition to case control studies, the current review will also incorporate case series so that additional risk factors may be presented.

Methods

MEDLINE, PubMed, Manual Alternative and Natural Therapy System (MANTIS), and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases were searched for the years 1966 through September 2006. Only peer-reviewed English language articles purporting to contain information on the subject of the etiology of CAD were selected for review. A series of searches was performed using the terms cervical artery dissection, vertebral artery dissection, and internal carotid artery dissection in combination with causation and risk factors using the AND Boolean operator. The literature generated by the searches was culled for relevant citations incorporated within the articles.

The selection criteria for incorporated articles consisted of case series, multiple case reports, cohort studies, and case-control studies that assessed pathophysiological CAD risk, while single case reports and letters were excluded.

Case-control studies were appraised for quality to determine which one provided the best estimate of association for each relevant risk factor. Appraisal was based on the size of groups, the use of matched controls, suitable recruitment methods, a reliable assessment of exposures, the potential for confounding, as well as the strength and precision of estimates.[14]

Results

The search strategy generated a total of 130 distinct citations, of which 49 were determined to be relevant after

applying the selection criteria that were outlined in the Methods section. An additional 6 references were harvested from the reference lists of the included articles. Table 1 provides a list of the available evidence pointing to CAD risk factors, including the study design and, when available, an estimate of association of what is deemed to be the best evidence.

Discussion

Connective tissue abnormalities

Persons with connective tissue abnormalities appear to be at increased risk of developing CAD because of an associated weakness in the arterial wall.[11,15] Brandt et al.[11] studied skin-biopsy samples of 65 patients with confirmed nontraumatic CADs and 10 control subjects via electron microscopy. Connective tissue abnormalities were present in 55% of the CAD patients (36 out of 65), based on abnormal skin biopsies, but none of the healthy control subjects. Structural abnormalities occurred in the extracellular matrix that were supposedly caused by basic molecular defects, which the authors suggested could be the primary genetic factor of many spontaneous dissections. Moreover, the majority of skin biopsies of CAD patients showed evidence of irregular collagen fibrils and fragmentation of elastic fibers. Interestingly, only three of the CAD patients had clinical manifestations of skin, joint, or skeletal abnormalities that could be detected on examination, making it difficult for clinicians to identify patients with connective tissue abnormalities who may be at increased risk for dissection.

The incidence of CAD has been reported to be higher in patients with Ehlers-Danlos syndrome, especially the vascular Type IV variant,[11,16,17] and Marfan syndrome.[18] These conditions are inherited connective tissue disorders that affect the skin, joints, and the walls of blood vessels.[19] Patients with these syndromes typically show signs of impaired skeletal integrity resulting in joint hypermobility, but in some cases, they only have vascular defects with minimal or no outward clinical manifestations. Patients with Ehlers-Danlos syndrome often report a history of easy bruising and may be identified by their physical appearance, which includes thin skin with visible veins; characteristic facial features, consisting of protruding eyes, small chin, thin nose and lips; and sunken cheeks.[19] Patients with Marfan syndrome also have a distinctive physical appearance that is characterized by facial features consisting of an extremely arched palate with crowded teeth, long limbs with spider-like fingers (arachnodactyly), chest abnormalities (e.g., pectus excavatum), and spinal curvature.[18]

Recent infection

Several studies have pointed to recent infection as a potential trigger of CAD,[20–22] although the relationship between infection and CAD is weaker when adjusted for the mechanical stresses associated with coughing, sneezing, and vomiting.[13] The underlying mechanism that connects recent infection with CAD is tentative, but arterial wall damage may be caused by proteolytic, oxidative, or autoimmune defects. A case control study found that acute infection was present in 31.9% of patients (15 of 47) with spontaneous CAD versus 13.5% of control subjects (7 of 52) who had an ischemic stroke from other causes. The crude odds ratio (OR) for this relationship was 3.0 (95% CI, 1.1 to 8.2), which was statistically significant $P = 0.032$. The association was much stronger in patients who experienced dissections involving more than one artery (OR 6.4; 95% CI, 1.7 to 24.0) than among those who had single artery dissections (OR 2.1; 95% CI, 0.7 to 6.3).[21] The authors suggested that the stronger relationship between infection and dissection in cases with multiple artery involvement as compared with those involving only a single artery may be a sign of a more serious underlying arteriopathy or an increased susceptibility to environmental factors or both.

The incidence of CAD has also been reported to be higher during certain seasons of the year, possibly related to the higher incidence of upper respiratory infections during the winter months. For example, Paciaroni et al.[23] reported that 31.3% (95% CI, 26.5 to 36.4) of their cohort of 352 CAD patients developed dissection in the winter, which was statistically significantly more than in the spring, 25.5% (95% CI, 21.1 to 30.3), the summer 23.5% (95% CI: 19.3 to 28.3), and the autumn 19.7% (95% CI: 15.7 to 24.1).

Hyperhomocysteinemia

Hyperhomocysteinemia may be a risk factor for CAD, especially in patients with total plasma levels that exceed 12 micromoles per liter.[24,25] The precise mechanism involved in this association is speculative; however, in vitro

Table 1 Available evidence pointing to risk factors for cervical artery dissection (CAD). The study design and estimate of association of what is deemed to be the best evidence is provided.

Risk factor	Available evidence	Study design	Estimate of association
Connective tissue abnormalities	Case-control studies. Brandt et al[11] reported 55% of 65 CAD patients showed abnormalities, whereas none of the control subjects did.	Case-control	None provided
Type IV Ehlers-Danlos syndrome	Case reports and series. CAD was found in 5 out of 202 Type IV Ehlers-Danlos patients.[17]	Case series	None
Fibromuscular dysplasia	Case reports and series. Present in 16 out of 126 CAD patients in a retrospective case series.[29]	Case series	None
Recent infection	Several case-control studies. The largest reported acute infection in 31.9% of 47 CAD patients versus 13.5% in non-CAD ischemic stroke control subjects.[21] The association was stronger in patients who had multiple artery dissections.	Case-control	Crude OR* 3.0 (CI† 1.1–8.2)
Hyperhomocysteinemia	Case-control studies. Significantly more CAD patients had homocysteine levels ≥12 micromol/L than control subjects.[26]	Case-control	64% of CAD patients, versus 13.9% of controls had homocysteine levels ≥12 micromol/L (CI 2.25 to 44.23)
Hypertension	Several studies have pointed to hypertension as a CAD risk factor. A well-designed case-control study reported a statistically significant association in the subgroup of CAD patients who developed cerebral infarction, especially in patients with VA dissection.[55]	Case-control	Overall OR 1.94 (CI 1.01 to 3.70) VA dissection patients OR 2.69 (CI 1.20 to 6.04)
History of migraine	Robust ORs have been generated in several case-control studies pointing to this association – the study that produced the largest OR compared CAD patients with a personal history of migraine with controls.[58]	Case-control	OR 7.41 (CI 3.11–17.64)
Cystic medial necrosis	Has been reported in numerous case studies.	Case reports	None

Type 1 osteogenesis imperfecta	Has been reported in numerous case studies.	Case reports	None
Anatomical abnormalities	Aortic root diameters >34 mm were present in 56% of cases versus 15% of controls.[51] Arterial redundancies have been identified in up to 65% of internal carotid artery dissections versus 12% of 187 non-CAD arteries. Eight out of 11 children with vertebrobasilar stroke had arcuate foramen.	Case-control	OR 14.2 (CI 3.2 to 63.6)
Autosomal dominant polycystic kidney disease	Has been reported in several case studies.	Case reports	None
Antithyroid autoimmunity	Antithyroid autoimmunity was present in 31.0% of 29 CAD patients, compared with 6.9% of 29 non-CAD stroke patients ($P = 0.041$).[62]	Case-control	None provided
EE genotype of the E469K ICAM-1 polymorphism	A case control study reported the EE genotype was more prevalent in CAD patients.[65]	Case-control	OR 3.16 (CI 1.14 to 6.96)
Methylenetetrahydrofol ate reductase C677T genotype	Conflicting reports. Not found to be independently associated with the occurrence of CAD in a case-control study, although it is associated with homocysteine levels.[67]	Case-control	No association
Alpha-1-antitrypsin deficiency	Conflicting reports. No association was found in a case-control study.[70]	Case-control	No association
Oral contraceptive use	Studies are in conflict. Only one small study showed that current use of oral contraceptives was associated with CAD. A more recent a larger study showed a non-significant association.[21]	Case-control	Non-significant association
Cardiovascular risk factors	Atherosclerotic changes, hypercholesterolemia, advanced age, and diabetes are reported to be either not associated or significantly less prevalent in CAD patients. One study found hypercholesterolemia to be present more frequently in the subgroup of patients who had ischemic events.	Case series and case-control	Mostly point to no association
* Odds ratio, †95% confidence interval			

studies have demonstrated that high levels of plasma homocysteine result in a decrease in the elastin content of the arterial wall, which negatively influences its elastic properties.[25] It is thought that hyperhomocysteinemia may be the result of a genetic predisposition, a nutritional deficiency, or a combination of these two factors. The strongest study to date in support of this relationship involved a group of 25 CAD patients which was compared to 31 non-CAD stroke patients who were less than 45-year-old, and a control group of 36 subjects. Sixty-four percent of the CAD patients (16 of 25) had homocysteine levels = 12 micromol/L, versus 13.9% of the control subjects (5 of 36).[26]

Hyperhomocysteinemia has been suggested as a potential risk factor for manipulation-related CAD because of the associated arterial wall abnormalities, which may increase the artery's susceptibility to mechanical stress.[25] Rosner[27] considered this association strong enough to suggest that assessment of homocysteine levels may be useful to identify patients who are at increased risk for experiencing movement-related CAD.

Fibromuscular dysplasia (FMD)

FMD is a rare nonatherosclerotic and noninflammatory vascular condition that primarily affects medium-sized arteries, in particular the renal and ICAs.[28] The condition is present in females 3 to 4 times more frequently than in males and occurs bilaterally in 65% of affected patients.[28] Most FMD patients are middle-aged when they are diagnosed. In the neck, FMD may at times affect the VA, but most commonly the ICA is involved.[29] The etiology of FMD is unknown, but there is some evidence that it may be related to mechanical stress to the arterial wall, ischemia within the vessel due to disturbance of the vaso vasorum, or hormonal activity that negatively affects the muscular wall.[28] Affected patients most commonly show a characteristic "string of beads" appearance on vascular imaging studies that is the result of irregular segments of stricture and dilation in the vessel. The condition is present in up to 23% of patients with ICA dissection; making it the most frequently reported associated abnormality.[30] FMD patients may have frank clinical manifestations consisting of transient ischemic attacks or cerebral ischemia, but at times they have less ominous symptoms such as headache and dizziness,[31] which may prompt them to seek chiropractic care. This phenomenon may account for confounding by indication, whereby adverse events from care are manifestations of the disease for which care was sought.

Cystic medial necrosis

Cystic medial necrosis has been reported in association with CAD in several studies.[32–35] It involves a focal degeneration of the elastic tissue and muscle of the tunica media, with the development of mucoid material. The term is actually somewhat inaccurate, because true cysts are not formed and there is no true tissue necrosis. Cystic medial necrosis is a nonspecific tissue defect that is associated with a variety of systemic disorders,[6] typically occurring in patients greater than 40-years-of-age at a ratio of two males for every female. It typically affects large arteries, chiefly the aorta, but is sometimes associated with the cervical arteries. In cystic medial necrosis, degenerative changes related to the aging process initiate a breakdown of the collagen, elastin, and smooth muscle, along with an increase in the artery's ground substance. Patients with Marfan and Ehlers-Danlos syndromes are especially prone to developing this condition.[36]

Osteogenesis imperfecta

Osteogenesis imperfecta is an inherited disorder that affects the bone structure leading to bone fragility that has been reported to be present in some CAD patients.[37,38] Other than having brittle bones, patients with this condition may present with a variety of other clinical features, such as blue sclerae, diminished hearing, thinness of the skin, and joint hypermobility. There is little agreement about the disease's definition and seven classifications and four degrees of severity have been described.[39] Type 1 is the form of osteogenesis imperfecta that has been reported to be associated with CAD because it interferes with the production of type 1 collagen. In some cases collagen synthesis is decreased, while in others, structurally defective collagen is produced.[38]

Arterial abnormalities

Arterial abnormalities are common in the cervical region, although their relationship with CAD is unclear. There have even been cases where one or both of the VAs are absent and the same is true regarding the ICA. Abnormalities may occur at any point along the course of these arteries, including atypical origin (e.g., the VA

originating from the aorta rather than the subclavian artery), hypoplasia (i.e., arteries with smaller than normal diameter), the VA entering the transverse foramen at levels other than C6, anastomoses between the VA and ICA, and others.[40] Some, but not all, of these anatomical variants may have a negative effect on cerebral circulation. For instance, Haynes[41] reported that the blood flow in 5% of the VAs of neck pain patients was significantly affected by contralateral cervical rotation, which was detected on Doppler ultrasonography.[42] The author suggested that these blood flow disturbances were related to unilateral arterial hypoplasia which did not permit adequate collateral circulation. Normally, when the blood flow from one VA is compromised, the opposite artery provides enough blood to adequately perfuse the posterior distribution.

The atlantal segment of the VA, where it is most vulnerable to injury associated with movement and is the usual site of dissection, is commonly anomalous. For instance, one study showed that 4 out of 5 cases who had occipitalization of the atlas also had an atypical pathway of the VA as it enters the cranium.[43] Another study that investigated the upper cervical region of 10 cadavers reported that the superior facet of the atlas was usually oval shaped with a groove on both sides of the facet, although some were kidney shaped with a groove only on one side. Accordingly, the shape, size and location of the VA groove was variable, as was the artery's course. In fact, no two arteries matched exactly in their course, in their length, or in their sizes.[44]

Cushing et al.[45] reported that eight out of 11 children with vertebrobasilar stroke had arcuate foramen. An arcuate foramen is the opening formed by the posterior arch of the atlas and a ponticulus posticus, which is a common anatomic variant that is present in from 3 to 15% of the population. The authors suggested that the VA may have become tethered in the foramen, predisposing them to dissection as a result of repetitive trauma associated with neck movement.

Arterial redundancies (e.g., coils, kinks, and loops) have been identified in up to 65% of CADs involving the ICA[46] and were found to be nearly twice as common in CAD patients with the aneurysmal form of dissection.[47] However, it is not known whether these abnormalities make patients more susceptible to manipulation-related dissection. Guillon[48] reported that the diameter of the common carotid artery was larger in patients with ICA dissection than in a group of matched controls, a factor which they thought might be an indicator of disturbed vessel wall integrity. Other ICA irregularities have been noted in the literature including a reversed position of the internal and external carotid arteries[49] and a low carotid bifurcation.[50]

Aortic root diameter enlargement was found to be significantly associated with CAD in a study that compared 28 consecutive CAD patients with 84 matched controls who had non-CAD related stroke. The cases in this study had aortic diameters > 34 mm 56% of the time (16 of 28), compared with 15% in controls (13 of 84). The OR was a robust 14.2 (95% CI, 3.2 to 63.6).[51] Another study that determined the origins of the VAs in dissection patients by angiography examined 860 left VAs and 717 right VAs. The authors reported that when the left VA was of aortic origin, it was associated with a significantly higher incidence of dissection than when the VA originated in the subclavian artery ($p < 0.001$). Another study that determined the origins of the VAs in dissection patients by angiography examined 860 left VAs and 717 right VAs. The authors reported that when the left VA was of aortic origin, it was associated with a significantly higher incidence of dissection than when the VA originated in the subclavian artery.[52]

Hypertension

Hypertension was shown to be a risk factor for CAD in several studies.[1,53–55] A well-designed case-control study by Pezzini et al.[55] compared the frequency of tobacco use, hypertension, diabetes, and hypercholesterolemia among a group of 153 consecutive patients with CAD, a group of patients with ischemic stroke that was not related to CAD, and a group of controls. Hypertension was the only one of these variables that was significantly associated with CAD, but only in the subgroup of CAD patients who developed cerebral infarction. The overall reported OR was 1.94 (95% CI, 1.01 to 3.70), and when dissection involved the VAs, the OR rose to 2.69 (95% CI, 1.20 to 6.04).

Migraine headache

Several studies have pointed to a history of migraine as a risk factor for CAD.[47,56–58] Tzourio et al.[56] carried out a hospital-based case-control study that involved 47 CAD

patients and 52 non-CAD related stroke patients who acted as controls. Among the CAD patients, 49.1% of them had migraine (23 of 47), while only 21% of controls did (11 of 52). The resulting adjusted OR was 3.6 (95% CI, 1.5 to 8.6). Another more recent hospital-based case-control study used prospective data collection methods to investigate a personal and a family history of migraine. The study involved three groups, which consisted of 72 CAD patients, 72 non-CAD related stroke patients, and 72 control subjects. A personal history of migraine, as well as a family history of migraine, was found to be positively associated with CAD. When specifically considering a personal history of migraine, the OR was 3.14 (95% CI 1.41–7.01) when the comparison was with the non-CAD stroke patients and 7.41 (95% CI 3.11–17.64) when compared with the controls.[58] A study that consisted of 71 CAD patients reported that those with the aneurysmal form of CAD had a higher rate of migraine than non-aneurysmal CAD patients.[47]

Autosomal dominant polycystic kidney disease (ADPKD)

ADPKD is a fairly common heritable condition, with a prevalence rate of 1 in 400 to 1 in 1000 persons. Besides affecting the renal system, the condition may also lead to extrarenal complications, including disorders of the connective tissues. ADPKD has been reported in association with CAD by several authors, although the frequency of this association and the mechanism involved is unknown.[59–61]

Recently identified pathophysiological mechanisms

Recent research from Pezzini et al.[62] suggests that autoimmunity may be involved in the process of local inflammation leading to the development of CAD. Moreover, the authors conducted a case-control study involving 58 subjects in which antithyroid autoimmunity was present in 31.0% of CAD patients (9 of 29), compared with 6.9% of non-CAD stroke patients (2 of 29) ($P = 0.041$). Based on these findings, the authors reasoned that immunologic mechanisms may contribute to the vascular damage that is thought to initiate arterial dissections.

There have also been recent reports of ICA dissection in patients with Graves disease, which is an autoimmune disease that results in hyperthyroidism.[63] The authors of this report on a pair of cases pointed out that thyroid hormones are known to have effects on the smooth muscle cells and endothelium of the vascular system, so it is plausible for this condition to predispose affected patients to dissection. The authors commented that this relationship has not previously been reported, possibly because CAD patients are not usually investigated for the presence of thyroid disease. Another study by Lucas et al.[64] reported that impaired endothelium-dependent vasodilation is present more frequently in CAD patients, which suggests that an underlying abnormality of the arterial wall layers may predispose to certain patients to CAD.

The EE genotype of the E469K ICAM-1 polymorphism was found to be more prevalent in CAD patients in a study that compared a primary group of 31 CAD patients, a secondary group of 65 CAD patients, and 204 healthy controls.[65] The OR for this relationship was 3.16 (95% CI, 1.14 to 6.96). The EE genotype gives rise to a pro-inflammatory tendency in patients that may predispose them to developing CAD. Similarly, C-reactive protein, which is a marker for inflammation, was investigated in a study that involved 62 patients with cerebral ischemia. The patients were divided into 3 groups based on the origin of the ischemia; CAD in 21 of the cases, atherosclerotic in 21, and of unknown origin in 20. There was also a control group that consisted of 54 age-matched healthy volunteers. The mean C-reactive protein level was 2.37 (95% CI, 0.57 to 4.78) mg/L in the CAD group, which was significantly higher than 0.54 (95% CI, 0.33 to 0.84) mg/L in controls, and 0.74 (95% CI, 0.14 to 7.86) mg/L in patients with strokes of unknown origin. Based on these findings, the authors thought that increased C-reactive protein levels in CAD patients supported the role of chronic infection in CAD pathogenesis.[66]

Pathophysiological mechanisms previously thought to be associated with CAD

Several genetic factors have been investigated that failed to show a strong association with CAD. The most promising is a mutation of the methylenetetrahydrofolate reductase C677T genotype (abbreviated *MTHFR*), which leads to elevated serum levels of homocysteine. Mutation of this genotype was initially reported by Pezzini et al to be strongly associated with CAD,[26] although subsequent better quality studies were not in agreement.[24,67] The issue remains controversial, however, because a recent study involving 174 CAD patients points to an associa-

tion. This study compared the proportion of *MTHFR* mutation among cases with previously reported data on 927 healthy controls. They found a weak relationship when the intact group was compared, which was more significant when a subgroup of 50 patients with multiple artery dissections were considered. Moreover, 18% of the patients with multiple dissections had the genetic defect (9 of 50) as compared with 10.6% of the healthy controls (98 of 927).[68]

Another genetic disorder that has been reported in association with CAD is Alpha-1-antitrypsin deficiency, which is a hereditary disease that may lead to liver disease and emphysema. Alpha-1-antitrypsin is a protein that inhibits the activity of enzymes, which if uncontrolled may weaken connective tissue. Accordingly, researchers have theorized that its deficiency may lead to a fragile vessel wall that is predisposed to dissection.[13] Its relationship with CAD was at first described in a small methodologically weak study,[69] but its findings were refuted by a more recent and methodologically sound study.[70] Another small study consisting of 12 spontaneous CAD patients found 3 cases with a deficiency of alpha-1-antitrypsin,[71] but overall, there is little evidence in support of this relationship.

Oral contraceptive use has been reported as being positively associated with ischemic stroke in general, even though most studies that have utilized newer products that contain lower doses of estrogen have not found an increased risk of stroke.[72] Nonetheless, a link between the use of oral contraceptives and CAD has been investigated because of the similarities between ischemic stroke and CAD-related stroke, and because both factors were thought to produce stroke in young patients. Only one study generated statistically significant findings via chi-square tests, which was a case-control study that investigated several possible CAD risk factors. The study reported that the current use of oral contraceptives was associated with CAD, whereas past contraceptive use was not.[57] However, this was a retrospective study and the analysis only involved 17 female cases and 24 female controls. Another case-control study that explored CAD risk factors found that 58.3% of CAD cases were using oral contraceptives (27 of 47), as compared with 40.0% of the controls who had ischemic stroke from another cause (21 of 52).[21] This finding was not statistically significant, however. Several other studies have considered the issue, but the consensus is that no good evidence exists supporting a clear-cut association.[20,58]

There is some evidence that common cardiovascular risk factors may actually have a protective effect on the development of CAD, although the matter has not been systematically studied. For instance, a study that involved 47 CAD patients and 52 non-CAD stroke control patients showed hypercholesterolemia to be significantly less prevalent among cases as compared with controls.[21] Another study involving 72 CAD patients who were compared with 72 non-CAD stroke control patients reported that diabetes, current smoking, hypercholesterolemia, and oral contraceptive use were not associated with CAD.[58] A case series comprised of 36 patients with spontaneous ICA dissections found atherosclerotic changes to be rare.[1] However, a descriptive study involving 181 patients who had 200 ICA dissections and another study from the same group of investigators that involved 169 patients with 195 VADs are at odds with most other studies that have considered hypercholesterolemia.[73,74] The authors reported that 55 patients with ICA dissection did not experience an ischemic event, while 145 of them did, and 116 of the ischemic patients progressed to a completed stroke. Interestingly, even though hypercholesterolemia is typically not associated with CAD, in this study it was present more frequently in the subgroup of patients who had ischemic events.

Limitations

There are several limitations to this review that may have influenced our conclusions. Although we searched several biomedical databases using various search terms, it is possible that relevant citations may have been missed. Another limitation is that case reports and series were included in this review, even though they offer very little information about the strength of an observed association and even less about causation. On the other hand, it is important for readers to become familiar with the risk factors for CAD, even those that are in the early stages of reporting. Case studies may also raise questions that prompt further investigation. All of the studies included in this review, including the case-control studies, employed observational research methods, which are not capable of determining causation. Thus, the risk factors mentioned herein are tentative until confirmed by stronger studies. A third limitation has to do with the narrative

review methodology that was used, which is less strict than that of a systematic review. For instance, we did not differentiate how many citations were obtained from each of the databases that were searched. Furthermore, reviews that do not use methodologically solid methods employed in systematic reviews are very susceptible to bias and confounding and serve mainly to discuss an issue rather than present an accurate summary of the literature. Both the strength and direction of association are suspect in narrative reviews since estimates are not likely reflective of overall results. Future research should investigate CAD risk factors using prospective designs involving substantially more patients. This would be difficult, however, given the rarity of the condition.

Summary

Many researchers think that an underlying arterial abnormality must be present in order for CAD to occur.[6,11,48,75] The most compelling pathophysiological CAD risk factors have to do with connective tissue abnormalities, which may contribute to a weakening of the vascular wall, making it more susceptible to tearing. Nonetheless, the exact pathogenesis of CAD is uncertain, especially in cases that occur spontaneously, are related to trivial trauma, or occur in the absence of discernable risk factors. Its etiology is probably multifactorial and related to a variety of arteriopathies that are produced by an assortment of genetic and environmental factors.[24,75] The clinical implications of the risk factors presented in this review are limited and it is still unknown which, if any, of them actually predispose patients to CAD following CSM. Furthermore, it is not possible to detect or predict CAD by screening patients for the presence of these risk factors and some of the tests are not practical in a clinical environment (e.g., genetic testing or skin biopsy). The ideal option for practitioners who are considering CSM is early detection of the disease through clinical examination for the presence of CAD signs or symptoms when possible, and through the use of Doppler ultrasound[76] and/or magnetic resonance imaging[77] when warranted. Patients with positive findings may require appropriate medical referral.[78]

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